UNIVERSITY OF LIVERPOOL

A better understanding of recent coronary heart disease mortality trends and determinants

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by

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‘A main cause of philosophical disease – a one-sided diet: one nourishes one's thinking with only one kind of example.’

Ludwig Wittgenstein

SUMMARY

Introduction

Coronary heart disease (CHD) is one of the leading global causes of morbidity and mortality. The underlying biological mechanisms are well understood, and a host of causal risk factors for the disease have been identified, mainly related to diet, smoking and physical activity. Evidence-based treatments for the disease are also available, reducing mortality and improving quality of life.

The decline in CHD mortality rates observed in most developed countries since the 1960s represents a most remarkable epidemiological phenomenon. However, this decline is not universal, and may now be in jeopardy. Thus, the mortality decline has recently plateaued in young adults in the United States. Furthermore, the absolute burden of disease is set to increase mainly because of an increasingly ageing population, and will represent a heavy burden to high, middle and low income countries alike. Furthermore, CHD incidence may rise in future because of recent adverse trends in major CHD risk factors, namely the worldwide increases in obesity and diabetes prevalence observed since the 1980s. Moreover, new technology and improved treatments are decreasing case fatality in CHD patients, increasing life expectancy and thus expanding the pool of patients surviving with clinically apparent disease. Finally, and crucially, important socioeconomic inequalities persist, perhaps reflecting disease determinants. The complex interplay of these factors and potential changes over time together suggest that the CHD epidemic may still be evolving. Further attention is therefore essential.

The analysis of time trends in disease specific mortality can thus potentially help us to understand the population dynamic of diseases such as CHD, warn about key changes and perhaps offer some novel insights for better prevention and control. However, most previous analyses have been focused on age-adjusted rates that might conceal important differences by age or by socioeconomic status, which might provide further understanding of trend drivers.

Aims and objectives:

My aim is to study recent coronary heart disease mortality time trends in different countries, in order to better understand the current state of the CHD epidemic. Furthermore, I will analyze the relative importance of CHD treatments and risk factors as drivers of the mortality trends. Finally, I will consider the Public Health implications of my findings.

My objectives therefore are:

1. To summarize our current understanding of Coronary Heart Disease (CHD) causation
2. To describe recent CHD mortality time trends focusing on age and gender specific trends by identifying periods with similar rate of change in diverse populations (England & Wales, the Netherlands, Poland and Australia).
3. To describe recent CHD mortality time trends by Socio-Economic Status in England and Scotland.

4. To quantify the role of risk factors and evidence-based treatments as drivers of the CHD mortality trends, first using a modelling approach in Poland, and then in England while also considering socioeconomic factors.
5. To consider the public health policy implications of dynamic trends in coronary heart disease mortality.

Methods

CHD mortality trends were analysed using the joinpoint regression approach. Widely used in cancer epidemiology, but rarely in CHD, this method explores trend data to find points in time ("joinpoints") that define segments where the trend has a constant pace of change. The key strength of this technique is objectivity- (it avoids the detection of potentially biased patterns when trends are described using time intervals defined subjectively by the researcher). Joinpoint avoids this potential bias by essentially removing the observer from the selection process, instead using a formal and objective exploration of the time-series data. My analysis therefore focused on age-adjusted rates, then age and gender specific rates. The analysis for Scotland and England also considered socio-economic status (using area-based measures of material deprivation).

The contributions of risk factors and treatments to the observed CHJD mortality trends in Poland were studied using the IMPACT model, a comprehensive, population-based model of CHD epidemiology. The model goal is to quantify the decline in coronary heart disease deaths in the Polish population between 1991 and 2005 which might be explained by risk factor changes and by treatments. The model is comprehensive, incorporating all usual treatments for coronary heart disease and heart failure plus all major cardiovascular risk factors, including smoking, blood pressure, cholesterol, diabetes, obesity and physical activity.

Similar analyses but also exploring the socio-economic differences were conducted in England, using a modified IMPACT model (IMPACTsec). That was used to estimate the contribution of risk factors and evidence based treatments to the observed decline in mortality in England between 2000 and 2007, for each quintile of the index of multiple deprivation.

Results

Age-adjusted trends in England and Wales, Scotland, Australia and the Netherlands conceal important recent age specific patterns. In these countries, the age-adjusted rates show continuing declines; however, among young adults a recent period of slowing down of the rate of decline in CHD mortality has been observed. Furthermore, trends are very dynamic, and the patterns can change surprisingly quickly. In the Netherlands, the sustained period of minimal change in young adults was followed by a period of further decline. Poland offers a strikingly different example of trend dynamism. After a period of constant increase, Poland showed a sudden, sharp decline in CHD mortality rates within a period of a very few years. This decline occurred in all age and gender groups, and still continues.

The recent mortality trends are probably attributable more to changes in risk factors rather than medical treatments. For example, using the IMPACT model to study the decline phase of the Polish

CHD epidemic, approximately 55% of the observed fall in mortality might be attributed to changes in risk factors, and only about a third to evidence based therapies.

Because of the social patterning of risk factors levels, further insights on the role of risk factors as major contributors to trend changes can be obtained by studying trends in levels stratified by socioeconomic circumstances. Scotland and England offer particular opportunities for detailed studies of trends in CHD mortality using high quality data including socioeconomic status. The resulting picture is complex. The recent flattening in CHD mortality trends observed in young adults was confined to the most deprived groups in Scotland, but was more uniform in England. A marked deterioration of medical care is implausible, meaning that the most likely explanation for this recent flattening of CHD mortality must be adverse trends in major cardiovascular risk factors.

The CHD mortality modelling in England produced intriguing results. As expected, socio-economic patterning of risk factor changes were observed. For example, decline in smoking levels contributed more to the observed decline amongst the more deprived groups. Social patterning was less clear among young adults in England. Moreover, the IMPACT SEC model analysis suggested that approximately half the CHD mortality fall was attributable to improved treatment uptake, with benefits occurring surprisingly equitably across all social groups. A similar analysis of the Scottish trends is therefore urgently needed to gain better insights on the drivers of the socioeconomic patterning underlying the observed trends.

Conclusions

The recent flattening in CHD mortality in young adults seen in many countries experiencing an overall decline in deaths strongly suggests that favourable trends can reverse. Furthermore, the rapid reversal observed in some age groups in the Netherlands and in the entire population in Poland suggests that recovery can occur very quickly.

These rapid mortality changes have been observed in many countries and cannot easily be dismissed as artefact. There is a strong case to mainly attribute these trends to changes in cardiovascular risk factors, since marked deterioration of medical care in these affluent countries appears implausible. This interpretation is also consistent with evidence from the rapid risk reductions observed in randomised drug and diet trials. Furthermore, several populations experienced “natural experiments” when socio-economic events producing beneficial effects on cardiovascular risk factors were rapidly followed by dramatic changes in CHD mortality.

These rapid mortality changes challenge some aspects of our current understanding of CHD causation. Specifically that the temporal relationship between changes in risk factors and changes in fatal outcomes are probably operating over much shorter timescales than previously assumed, within a few years rather than decades.

The public health implications of these findings are thus clear: large changes in CHD burden can be achieved quickly, probably reflecting trends in dietary and other cardiovascular risk factors. Population level prevention interventions might therefore be both powerful and rapid.

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This thesis is not just a narrative of a journey of discovery while mastering a narrow field of scientific enquiry. It has also been a personal journey for me, my friends and my family.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABREVIATIONS

AAPC	Average annual percent change
AMI	Acute myocardial infarction
APC	Annual percent change
BIC	Bayesian Information Criterion
BMI	Body Mass Index
CABG	Coronary artery bypass surgery
CHD	Coronary heart disease
CVD	Cardiovascular disease
DALY	Disability adjusted life years
DM	Diabetes Mellitus
DPP	Deaths prevented or postponed
g	grams
GBD	Global Burden of Disease Study
HDL	High-density lipoproteins
ICD	International classification of diseases
IMD	Index of Multiple Deprivation
LDL	Low Density Lipoproteins
LSOA	Lower Layer Super Output Area
MI	Myocardial infarction
mmHg	millimetres of mercury
mmol/l	millimoles per litre
MRFIT	Multiple Risk Factor Intervention Trial
ONS	Office of National Statistics, UK
PARF	Population attributable risk fraction
PSC	Prospective Studies Collaboration
PT	Permutation test
PCI	Percutaneous coronary intervention
RCT	Randomized Controlled Trial
SBP	Systolic blood pressure
SFA	Saturated fatty acids
SIMD	Scottish Index of Multiple Deprivation
UK	United Kingdom
USA, US	United States of America

LIST OF PAPERS (PUBLISHED AND SUBMITTED) AND STATEMENT OF AUTHORSHIP

1) O'Flaherty M, Ford E, Allender S, Scarborough P, Capewell S. Coronary heart disease trends in England and Wales from 1984 to 2004: concealed levelling of mortality rates among young adults. **Heart 2008**; 94(2):178-181.

   Roles: As first author, I participated in the study design, and led the data analysis, manuscript drafting and critical revision.

   (CHAPTER 5)

2) O'Flaherty M, Allender S, Taylor R, Stevenson C, Peeters A, Capewell S. The decline in coronary heart disease mortality is slowing in young adults (Australia 1976–2006): A time trend analysis. **International Journal of Cardiology 2011;** (epub ahead of print: doi:10.1016/j.ijcard.2011.01.016)

   Roles: As first author, I participated in the study design, and led the data analysis, manuscript drafting and critical revision.

   (CHAPTER 5)

3) Vaartjes I, O'Flaherty M, Grobbee DE, Bots ML, Capewell S. Coronary heart disease mortality trends in the Netherlands 1972–2007. **Heart 2011**; 97(7):569-573.

   Roles: As co-author, I made a major contribution to study design, supervision, further data analysis and interpretation, manuscript drafting, critical revision and finalization.

   (CHAPTER 5)

4) Bandosz P, O' Flaherty M, Drygas W, Rutkowski M, Koziarek J, Wyrzykowski B, Bennett K, Zdrojewski T, Capewell S. Analysing the decline in coronary heart disease mortality in Poland after socioeconomic transformation. **BMJ 2011**; (accepted for publication August 2011)

   Roles: As second author, I made a major contribution to study design, critical analysis of data sources, the development and implementation of the Polish version of the IMPACT Model, drafting, critical revision and finalizing of the manuscript.

   (CHAPTER 6)

5) O'Flaherty M, Bishop J, Redpath A, et al. Coronary heart disease mortality among young adults in Scotland in relation to social inequalities: time trend study**. BMJ. 2009**;339:b2613.

   Roles: As first author, I participated in the study design, and led the data analysis, manuscript drafting and critical revision.

   (CHAPTER 7)

6) Bajekal M, O'Flaherty M, Scholes S, Raine R, Norman P, Capewell S. Trends in CHD mortality by socioeconomic circumstances, England 1982-2006. (Submitted to BMJ)

   Roles: As second author, I made a major contribution to study design, data analysis, manuscript drafting, critical revision and finalization.

   (CHAPTER 7)

7) Bajekal M, Scholes S, Love H, Hawkins N, O'Flaherty M, Raine R, Capewell S. Explaining recent socioeconomic trends in coronary heart disease mortality in England, 2000-2007. A population modelling study. (Submitted to PLoS Medicine)

   Roles: As co-author, I participated extensively in the study design, development of the extended version of the IMPACT model, data analysis, manuscript drafting, critical revision and finalization.

   (CHAPTER 7)

8) Capewell S, O'Flaherty M. Rapid mortality falls after risk-factor changes in populations. **Lancet 2011**; 378(9793):752-753.

   Roles: I jointly developed the concepts with Prof Capewell and jointly drafted the manuscript.

   (CHAPTER 8)

9) Capewell S, O'Flaherty M. Can dietary changes rapidly decrease cardiovascular mortality rates? **European heart journal. 2011;** 32(10):1187-9

   Roles: As co-author, I jointly developed jointly with Prof Capewell the concepts and drafted the manuscript.

   (CHAPTER 8)

1 INTRODUCTION

Cardiovascular disease (CVD) and particularly coronary heart disease (CHD), is one of the leading global causes of morbidity and mortality. The underlying biological mechanisms are well understood, and a host of risk factors for the disease has been identified, mainly during the 20th century. Effective treatments for the disease are also available, reducing mortality and the substantial impairments imposed by these diseases on quality of life and wellbeing.

Our substantial knowledge on causes and treatment suggest that the disease can fall to a point far below its current mass occurrence, if not reach an ideal minimal endemic level.

The decline in CVD mortality rates since the 1960s has been one of the most remarkable phenomena in epidemiology. However, this decline may now be in jeopardy. The absolute burden of disease is set to increase mainly because of an increasingly ageing population. Furthermore, CVD incidence may rise because of adverse trends observed in major risk factors for the disease, namely the worldwide increase in obesity and diabetes prevalence observed since the 1980s. Furthermore, new technology and improved delivery of existing treatments are decreasing case fatality, increasing life expectancy and thus, increasing the pool of people remaining alive but with clinically apparent disease.

The complex interplay of these factors is conceivably the main driver of CVD disease burden in a population. If so, this interplay then has direct implications for the potential preventative and therapeutic options available to tackle the heavy burden of CVD in so many populations.

The analysis of time trends in disease specific mortality can thus potentially help us to understand the population dynamic of these diseases, warn about key changes and perhaps offer some novel insights for better control.

1.1 AIMS

My aim is to study recent coronary heart disease mortality time trends in different countries, in order to better understand the current state of the CHD epidemic. Furthermore, I will analyze the relative importance of CHD treatments and risk factors as drivers of the mortality trends. Finally, I will explore the Public Health implications of my findings.

1.2 OBJECTIVES OF THIS THESIS

1. To summarize our current understanding of Coronary Heart Disease (CHD) causation
2. To describe recent CHD mortality time trends focusing on age and gender specific trends by identifying periods with similar rate of change In England & Wales, the Netherlands, Poland and Australia.
3. To describe recent CHD mortality time trends by Socio-Economic Status in England and Scotland.
4. To quantify the role of risk factors and evidence-based treatments as drivers of the CHD mortality trends, first using a modelling approach in Poland, and then also considering socioeconomic factors in England.
5. To explore the public health policy implications of dynamic trends in coronary heart disease mortality.

2 CORONARY HEART DISEASE

2.1 INTRODUCTION

Coronary heart disease encompasses a range of clinical syndromes that have as underlying aetiology progressive atherosclerosis of the coronary arteries supplying the myocardium. This phenomenon consists of the development of “plaques” in the wall of arteries. These plaques undergo extensive inflammatory, thrombotic and metabolic changes that result in the impairment of myocardial blood flow over a range of timescales, from chronic progressive restriction of the blood flow to sudden occlusion.

2.2 BIOLOGY, NATURAL HISTORY AND CLINICAL ISSUES

2.2.1 Atheromatosis

Atheroma is one of the lipid storage disorders. Over the last century, evidence has emerged suggesting cholesterol as a crucial factor in its formation.[1] Low density Lipoproteins (LDL) transports blood cholesterol, which then enters the arterial intima. There the LDL molecules become oxidized and can act as potent promoters of the atherogenesis process. This process includes the induction of endothelial and smooth cell activation, secretion of inflammatory mediators and expression of adhesion molecules, leading to leukocyte accumulation in the subendothelium. This inflammatory response in turn can promote further oxidation of the LDL particles and resulting in the activation of macrophages that engulf the LDL particles to become “foam cells” (cells loaded with lipids). These activated macrophages can then further contribute to damage by various secreted mediators or by adding thrombogenic and antigenic debris to the lesion, fostering the progress of the resulting atherosclerotic plaque.[2]

Additionally, macrophages can present fragments derived from oxidized LDL particles as antigens to recruited T cells, an activity that supports the crucial role of lipids both in innate and

adaptive immune responses in atherosclerosis.[2] This is a crucial feature of atheromatous disease, as lipid metabolism and thrombotic and inflammatory mechanisms are closely linked.

2.2.2 Clinical Syndromes

The obstruction of blood flow in the coronary arteries might result in diverse clinical syndromes. The atherosclerotic build up in the coronary arteries may start very early in life[3,4] and the disease can manifest itself with symptoms of chronic obstruction of the blood flow to the myocardium, resulting in anginal chest pain (Chronic Stable Angina). However, thrombotic and inflammatory phenomena shorten dramatically the timescales for the evolution of the disease by making the atheroma plaque unstable. This in turn could result in thrombosis and the development of acute obstructions to the blood flow, known as the acute coronary syndromes. Depending on the amount of myocardium muscle compromised, these syndromes are further subdivided in myocardial infarction (with and without ST elevation) and unstable angina. But perhaps the most dramatic consequence of sudden occlusion of the coronary arteries is the occurrence of ischemia induced malignant cardiac rhythm disturbances resulting in Sudden Cardiac Death. This is often the first clinically evident manifestation of the disease. Here, few therapeutic options other than prevention are available.

The life expectancy of people developing any form of CHD is substantially reduced, and their quality of life is also significantly decreased[5], suggesting that preventing CHD events from happening in the first place is potentially associated with a significant reduction in disease burden. Furthermore, because one of the main consequences of atherosclerotic obstruction is the loss of myocardial muscle, a common occurrence in many of these patients is the subsequent development of heart failure, a condition with particularly high mortality, poor quality of life and with high consumption of healthcare resources.

2.3 PUBLIC HEALTH IMPORTANCE

CHD and CVD both exert a heavy burden on society. They consistently feature among the leading causes of morbidity and mortality in both developed and developing countries. CHD has a profound impact on resource use, is associated with profound health inequalities and causes an inordinate amount of impaired quality of life.

Interestingly, our knowledge about CHD causation, prevention and therapeutic strategies is extensive, indeed it epitomises evidence-based medicine.

2.3.1 The UK Burden

In 2007, there were approximately 193,000 deaths attributable to cardiovascular disease, representing some 34% of the total deaths in the UK. Of these, almost 90,000 were attributed to CHD, meaning that one in five deaths in men and 1 in six deaths in women could be attributed to CHD. [6]

Crucially, CHD is the main cause of premature mortality (under 75 years). In the UK, 19% of and 10% of premature deaths in men and women are due to CHD.[6] Age is commonly considered a non-modifiable risk factor for the disease. CHD has strong age gradients, and the disease is rare under 30 years of age, but increasingly common above the age of 60.[7]

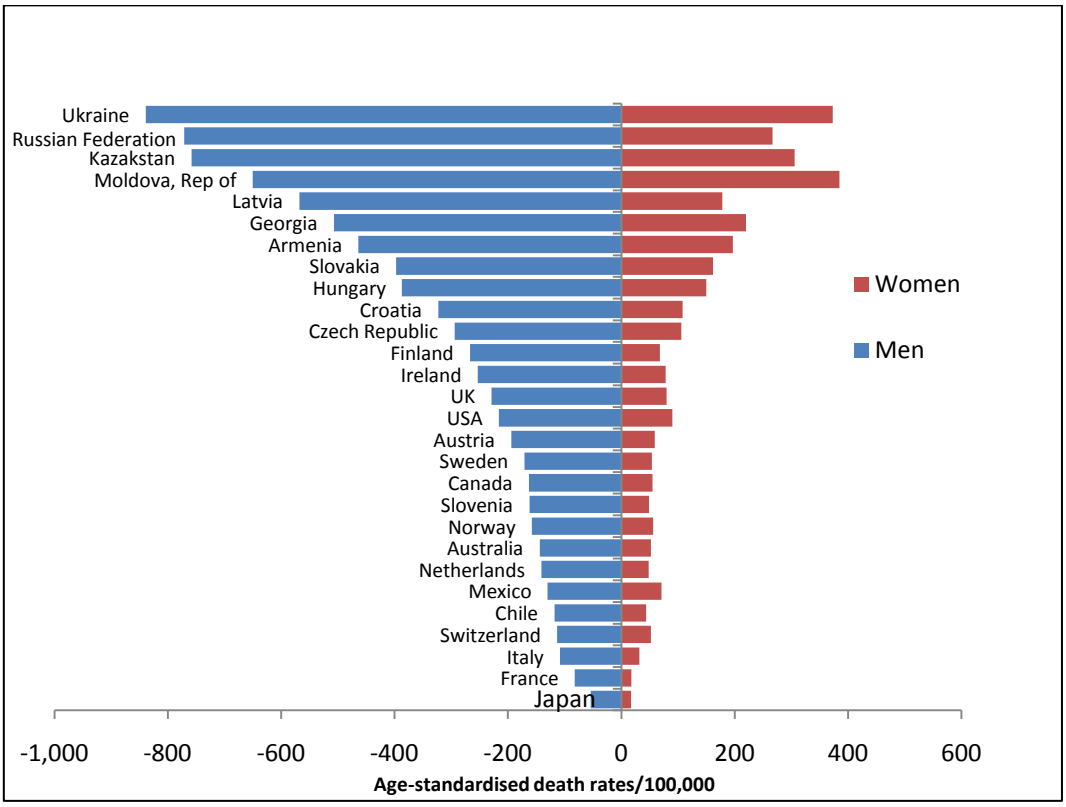
There are also strong socio-economic gradients with premature death rates being up to threefold higher in deprived groups compared to more affluent groups, making CHD and stroke key targets for reducing inequalities.[5]

CHD prevalence generates a substantial disease burden to society, and more than 3 million people in the UK currently suffer from CHD.[6] Total annual UK costs for CHD exceed £10billion, with recent NHS costs of £3.2 billion and still rising. An additional £1 billion was recently spent on NSF initiatives, like promoting a healthier lifestyle, providing statins in the secondary and primary prevention setting, improving the delivery of key services like acute revascularization and cardiac rehabilitation.[5,8] Substantial indirect costs also are incurred each year, mainly related to productivity losses (2006: £3.9 billion) and informal care (£1.8 billion).[8]

2.3.2 Global Burden

Coronary heart disease mortality rates for both men and women vary substantially between different countries (figure 2-1). For example, in Europe, men in former Soviet Union Republics like the Ukraine have CHD mortality rates that are about 7 times higher than rates observed in France or Japan, countries with some of the lowest mortality rates in the World.

Figure 2-1 CHD mortality rates in selected countries (year 2000, rates per 100,000) Source: WHO mortality database



The Global Burden of Disease Study (GBD) estimated in 2004 that about 7.2 million deaths were attributed to CHD, comprising 12% of total deaths. This effectively ranked CHD as the most common cause of death globally, in high and medium income countries. In low-income countries, CHD is the second most common cause of death, after lower respiratory infections. However, about 80% of the CHD burden now happens in low and middle-income countries. [9]

Because age is a major factor associated with CHD mortality and morbidity, the burden of disease is expected to increase globally -particularly in low and middle-income countries- simply because of population ageing. Therefore, CHD will continue to be the leading cause of death in 2020 and even 2030.[9] Interestingly, despite the current decline in CHD Mortality rates in high income countries, current GBD projections still considers CHD as the leading cause of death in the next 3 decades.

CHD is amongst the leading six causes of death and disability when taking into account age at death and age effects on disability in a metric known as DALY (disability adjusted life years), and the second cause in middle and high-income economies. Thus, major increases are also expected in low-income countries, as their population ages.[9]

2.4 CONCLUSIONS

Coronary heart disease is an important disease for low, middle and high-income countries. This burden is increasing in part because of the progress in the control communicable diseases and injuries, leading to an increased life expectancy. Treating and managing the disease is consuming an increasingly large amount of resources both directly and indirectly, and causing a significant impact on individuals, their families and the society.

Unravelling the biological basis of the atherosclerotic process has helped us to better understand the complex clinical presentations of the disease. In the next section, I will briefly consider the aetiology of coronary heart disease, perhaps one of the most studied diseases in human history, with over a century of accumulating scientific evidence. The development of the risk factor paradigm has been essential to understand the causes and potential control strategies for CVD, as I will discuss in the next chapter.

3 THE RISK FACTOR PARADIGM FOR CVD CAUSATION

3.1 INTRODUCTION

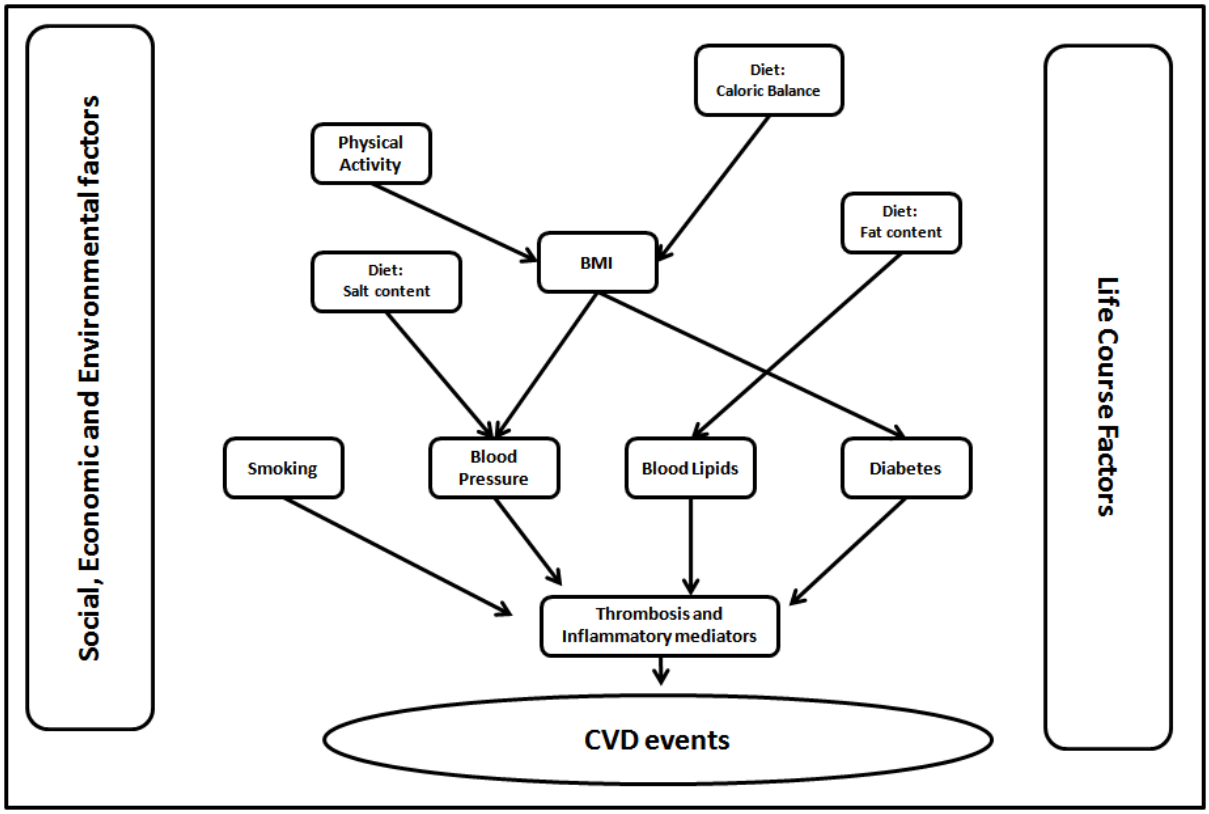
During the 20th century, we acquired considerable knowledge about causation of coronary heart disease. As discussed in chapter 2, the main pathophysiological phenomenon is vascular atherosclerosis, the progressive narrowing of arteries by the atherosclerotic plaque. This plaque is a complex structure, the result of endothelial dysfunction, blood lipid accumulation and the subsequent host inflammatory and thrombotic responses.[2]

Many factors are causally related to the development of arterial atherosclerosis (Figure3-1), and the landmark Framingham study identified most of them.[10] The major biological risk factors are causally proximal to events. However, important determinants of disease including diet or socioeconomic circumstances are more distally related and influence CHD risk by indirect pathways through the more proximal risk factors, and also by direct links to events.

There is also a growing body of evidence that links early life developments, childhood and adolescent trajectories and adult levels of risk factors. This suggest that the causation of coronary disease develops over the life course, but that early ages are particularly important.[11]

Furthermore, evidence of atherosclerosis has been found in autopsies of teenagers and young adults[3], suggesting that the atheromatous process ending in clinically apparent coronary events might take decades to develop.[12,13]

Figure 3-1 Causal pathways in coronary heart disease



3.2 MAJOR ESTABLISHED RISK FACTORS

The idea of cardiovascular risk factors developed over the mid 20th century, particularly after a landmark paper from Framingham by Kannel et al.[14] This initial insight was widely confirmed with a host of subsequent observational and experimental studies.

The Framingham study started in 1948 to explore the causal relationship between several physical and biochemical traits and cardiovascular disease. This was a cohort study recruiting 5209 men and women aged 30 to 62 from the town of Framingham in Massachusetts, United States. The participants were followed up and the occurrence of CVD events was recorded, with detailed clinical and biochemical examinations conducted every two years. Initially, this study identified raised blood cholesterol, raised blood pressure, and tobacco use as major risk factors for CHD.[14,15]

During the 1950s, the Seven Countries Study studied the relationship between biological and lifestyle risk factors in a wider set of populations, by conducting 16 cohort studies in seven countries,

in four regions of the world (United States, Northern Europe, Southern Europe and Japan), and addressed the important question of replicating the association of risk factors with CVD outcomes in other settings. This study included countries with high and low mortality rates, confirming the relevance of the Framingham risk factors, but suggesting a variable importance of the associations.[16] This study was also the first to identify important dietary patterns, and how the adoption of less healthy diet can result in increased CVD risk.[16] Later studies, like the Nurses' Health Study, a large cohort study of nurses in the United States have helped to confirm the importance in women of the already identified major cardiovascular risk factors, particularly regarding obesity, physical activity, diet and hormonal factors.[17]

Later, during the 1980s and 1990s, the MONICA Study using carefully designed protocols and methods and exquisite attention to detail, was able to explore more precisely the contribution of risk factors and treatments to mortality trends in over 20 diverse populations.[18,19] The MONICA Project goals were to measure the trends in cardiovascular mortality and coronary heart disease and cerebral-vascular disease morbidity and to assess the extent to which these trends are related to changes in known risk factors, daily living habits, health care, and major socioeconomic features measured at the same time in defined communities in different countries. Their main findings were that about one third of the change in CHD mortality rates could be attributed to health care and two thirds to changes in risk factors. I will discuss later in more detail their results (see chapter 4).[19,20]

The concept of risk factor for cardiovascular disease is firmly rooted in the way causal factors are addressed in epidemiology, using guiding principles like those developed by Bradford Hill.[21] Using these criteria, an association is considered causal if it is strong and shows a biological gradient, it is found consistently over a range of contexts, it is specific and the exposure precedes the outcome, and it is not due to chance. Finally and crucially it has to be unconfounded and verified experimentally.

Recent adaptations of these criteria have simplified the concept. First, we should obtain direct evidence from experimental or observational studies showing that a probabilistic association between intervention and outcome is causal and not due to chance or bias, preferably supported by an experiment or trial. This is further supported by evidence of a dose-response and the strength of the association, when experimental evidence is not available. Second, one requires evidence of a clear biological mechanism linking the alleged causal web that links the putative risk factor and the outcome. Finally, parallel streams of evidence supporting the causal hypothesis suggested in one study, with comparable studies in various contexts showing similar results.[22]

The large cohort studies I have discussed before provided most of the evidence necessary to assert causality within this framework. This was later confirmed when experimental evidence available at the time of the development of interventions to decrease risk factors levels started to emerge.[23,24] Subsequent support came by similar findings across a range of populations and settings, using a variety of observational approaches.[25-27]

Understanding the evidence base for CVD causation is essential, firstly for knowing what drives trends in the disease burden of disease and secondly to provide evidence for disease control policies. In the following sections, I will briefly describe the evidence to understand the causation of CVD for the major risk factors (summarized in Table 3-1 and 3-2).

3.2.1 Smoking

The report from the US Surgeon General in 1964 suggested that smoking was a clear risk factor for lung cancer and chronic bronchitis, but was less emphatic in describing its relationship with CVD risk, suggesting that although risk increases in smokers, the association has not been at that time, to be proved causal.[28]

However, over the years from that report a large body of evidence linking tobacco smoking to changes in inflammatory and thrombosis markers and with subclinical markers of atherosclerosis was accrued.[29] This body of evidence suggest a clear link between smoking and basic atherosclerotic disease mechanisms.

Previous US Surgeon general reports have summarized the extensive body of evidence linking tobacco smoking with CHD, increasing its risk by almost twofold.[30] They also confirmed its harmful effects in women and demonstrated a dose-response relationship.[29]

Table 3-1 Summary of the evidence base for the major modifiable biological risk factors for coronary heart disease

Risk Factor	Effect Size	Temporal relationship	Strength	Dose-Response relationship	Experiment	References
High Blood Cholesterol	1 mmol/L lower total cholesterol was associated with reductions in coronary heart mortality ranging from about 50% in men and women aged 40-49 and 17% in those 70-79 , across the range of cholesterol	Observational and RCT evidence	Observational and RCT evidence	Observational and RCT evidence	Blood lipid reduction therapies RCTs showed that reducing blood lipids levels is associated to a reduction in fatal and non fatal CVD events	Lewington 2007, [26]; Law 2003[24]
High Blood Pressure	A difference of 20mmHg in SBP was associated to more than twofold differences in stroke mortality and two fold differences in ischemic heart disease mortality	Observational and RCT evidence	Observational and RCT evidence	Observational and RCT evidence	Antihypertensive treatments RCTs showed that reducing blood pressure levels is associated to a reduction in fatal and non fatal CVD events	Lewington 2002 [25];He 1999[31]
Smoking	Between 2.5 to 3.3 times increased risk in smokers compared to non smokers.	Observational evidence	Observational evidence	Observational evidence	No	US Dept of Health 2004[29]

Table 3-1 (continued)

Risk Factor	Effect Size	Temporal relationship	Strength	Dose-Response relationship	Experiment	References
Diabetes Mellitus	increasing risk by 2.4 times in men and 5.1 times in women	Observational evidence	Observational evidence	Observational evidence	Observational evidence, RCTs showed effects on nonfatal MI events but not on stroke or mortality outcomes.	Wilson 1998[32];Kannel 1985[33]
Obesity	Independent effect small, most of its effects is mediated through other risk factors.	Observational evidence	Observational evidence	Observational evidence	No	The Emerging Risk factors collaboration 2011[34]
Lack of physical activity	Increase risk	Observational evidence	Observational evidence	Observational evidence	No	Warburton 2006[35]

More recently the INTERHEART study, a large international case control study including 50,000 participants with incident acute myocardial infarctions (AMI), reported that the risk of AMI among smokers was 3.3 in young adults and 2.5 in older adults.[27] The health effects of passive smoking have been also solidly established, with a relative risk for CHD of 1.26 to 1.65.[36,37] More importantly, data from systematic reviews in tobacco cessation studies after MI, showed marked reductions in risk, of almost 40% within two years.[38,39]

In conclusion, the association between smoking and cardiovascular disease is strong, graded and unconfounded.

3.2.2 Blood Lipids

More than a century ago, Virchow first suggested the association of blood lipids and atheromatosis. This was supported by animal feeding experiments conducted by Anitschcov early in the 20th century. Observational evidence from migrant studies, the Seven Countries study [16] and the Framingham study[14,15] found the association in humans, confirmed later in MRFIT[40], PROCAM[41] and ARIC[42] studies. The development of lipid reduction therapies, particularly HMG-CoA Reductase inhibitors (statins) provided experimental evidence of causality, not without some controversy.[24,43]

Total cholesterol is clearly associated with CHD risk, as summarised in the Prospective Studies Collaboration systematic review and meta-analysis, a large systematic review summarizing 61 cohorts consisting of almost 900,000 adults without previous disease, with nearly 12 million person-years of follow-up, and more than 50,000 vascular deaths. In this study, a 1 mmol/L lower total cholesterol was associated with reductions in coronary heart mortality ranging from about 50% in men and women, aged 40-49 and 17% in those 70-79 , across the range of cholesterol levels in most developed countries, and showing a linear relationship, with no evidence of a threshold.[26]

Statins effectively reduce cholesterol levels between 1.8 and 2.8 mmol/l (depending on drug and dose) and this translates into cardiovascular event reductions. Reductions of 1 mmol/l are associated with a reduction of ischemic heart disease risk by 11% in the first year of treatment, 24% in the second year, 33% in years three to five, and by 36% thereafter, clearly indicating that substantial reductions in events can happen very quickly. [24]

High-density lipoproteins (HDL) represent another important lipid sub-fraction; they are protective and have a strong inverse association with CHD events. Thus, increases of 1 mg/dl are

associated with 2-3% reductions in total CVD risk.[44] Interestingly, randomized clinical trials of novel drugs aimed to increase HDL levels have thus far failed to show any reduction in CVD risk.[45]

Triglycerides have been associated to CVD risk, but their levels tend to reciprocate HDL concentrations. Their role as an independent risk factor remains controversial, and current control strategies only target them in special cases.[46]

Dietary saturated fats are the main determinants of blood lipids levels, particularly total cholesterol.[47] However, not all dietary fats are harmful. Mono-unsaturated fatty acids, (olive oil), poly-unsaturated fatty acids (marine omega 3 fatty acids) and plant-based omega 6 fatty acids, are associated to lower CVD risk, particularly when replacing saturated or trans-fats.[48-50]

3.2.3 Blood Pressure

Numerous observational and experimental studies have linked high blood pressure with adverse cardiovascular outcomes over the last decades. Moreover, the link between endothelial dysfunction, vascular remodelling and hypertension with subsequent atherosclerosis progression has been clearly defined at the metabolic and functional levels.[51,52]

Diastolic blood pressure (DBP) has been identified as an independent, graded and important predictor of CVD risk in large, prospective cohort studies and randomized clinical trials.[53-55] However, later studies focused on exploring the association of systolic blood pressure (SBP) and risk, which resulted in even a stronger association compared with diastolic blood pressure. The Prospective Studies Collaboration systematic review produced a good summary of the evidence.[25] This was a large systematic review involving 61 prospective studies observing 12,7 million person-years at risk and with 56,000 vascular deaths. For each difference in 20mmHg, SBP was associated with almost a threefold difference in stroke mortality and a twofold difference in ischemic heart disease mortality. Interestingly, the relationship was linear down to a SBP as low as 115mmHg. Although the risk attenuated in those 80 years and older, the absolute difference in event rates was biggest in older ages. Reduction of blood pressure and crucially SBP significantly reduce vascular events and deaths in people free from vascular disease. The CVD and CHD risk associated with blood pressure has been also found in many other populations.[56]

In a systematic review and meta-analysis, He and Welton[31] found a statistically significant risk reduction of 21% in CHD events and deaths, and a reduction of 27% in CHD mortality.

Antihypertensive treatments reduce stroke risk more substantially, with a 37% reduction in total events and a 36% reduction in fatal strokes. Similar findings have been reported by Law et al.[23]

Dietary Salt intake is a major determinant of blood pressure levels.[57,58] Furthermore, a large body of evidence suggests that salt consumption is probably the single most important factor in determining blood pressure levels. The biological mechanisms has been explored in animal studies, and epidemiological evidence has been found in ecological studies like INTERSALT[59] or INTERMAP[60] and in the prospective cohort study EPIC-Norfolk.[61] The INTERSALT Study was a standardized, worldwide epidemiologic study of large sample size (n = 10079 men and women aged 20-59 y from 32 countries) that studied both within- and cross-population ecological association between 24-h sodium excretion (a proxy for salt intake) and blood pressure. The estimated effect of a sodium intake higher by 100 mmol/d was higher blood pressure by approximately 3 to 6 mmHg of SBP and to 0-3 mm Hg of DBP. This relation prevailed for both men and women, for younger and older people, and for participants without hypertension.[59] The INTERMAP study, with improved exposure and outcomes measurements, confirmed the association at the individual level with greater detail, although for a more limited set of countries.[60] The EPIC-Norfolk study was a large cohort study conducted in Norfolk, UK, recruiting 30,000 participants with the aim of looking at the association between diet and lifestyle risk factors and cancer, but with the secondary aim of looking to cardiovascular outcomes. They found that individuals with salt intakes below 5 g per day halved their risk of developing high blood pressure compared to those at high intakes (10 g per day or more).[61] Interestingly, they also found that high intake of dietary potassium was associated to lower blood pressure.[61]

Experimental evidence supporting the causality of the association of SBP and salt consumption came from population-based intervention studies. Forte et al tested the effect of an educational campaign on salt intake in two matched communities in Portugal.[62] In the intervention community average blood pressure fell by 3.6/5.0 mmHg at one year and 5.0/5.1 mmHg at two years. Although other community interventions trials failed to observe changes in salt consumption, they also reported lack of change in blood pressure levels.

More interestingly, the effect of salt on cardiovascular outcomes has been explored in RCTs. The THOP I and II studies[63] randomized about 3000 participants to a sodium reduction intervention or a control, and followed up to 15 years after the termination of the studies. They found that a reduction of salt intake resulted in a SBP fall between 1.2 and 1.7 mmHg and a 25% risk reduction in cardiovascular events over 10 to 15 years.

The focus on salt reduction initiatives across entire populations has been probably one of the most important drivers in decreasing blood pressure levels in many populations.[57,58,64]

3.2.4 Obesity

Obesity and overweight are conditions associated with an imbalance in energy intake and expenditure. The current physical, cultural and marketing environments are a powerful determinant of the continuing increases in obesity prevalence reported in the late 20th century and early 21st century.[65]

Adipose tissue is metabolically active and can release a host of mediators that control body weight homeostasis and insulin resistance. Crucially, it also influences inflammation and thrombotic pathways leading to endothelial dysfunction and atherosclerosis.[66] Not surprisingly thus, obesity is strongly associated with CVD risk factors and diabetes[67], and is associated with excess mortality, mainly attributable to CVD and several common cancers.[68-70]

However, the independent effect of obesity is probably small[34], suggesting that most of its associated risk is mediated by more proximal risk factors, like systolic blood pressure, elevated cholesterol and diabetes.

3.2.5 Diabetes Mellitus

Diabetes mellitus (DM) is a risk factor for CHD, increasing risk by approximately 2.4 times in men and 5.1 times in women.[32,33] It also has been identified in the early stages of atheroma formation in young ages[71], and negates the low risk otherwise experienced by pre-menopausal women.[72] Patients with diabetes have similar rates of events as patients with CHD but without diabetes.[73] All levels of abnormal glucose metabolism are associated with cardiovascular disease, primarily by diabetes induced arterial macro-vascular atherosclerotic disease.[74]

The mechanisms leading to enhanced development of atherosclerosis in diabetic persons are complex, and likely involve endothelial dysfunction, inflammatory mediators and modification in lipid metabolism.[75]

Hyperglycaemia has also direct endothelial toxicity, leading to atherosclerosis.[76] This direct mechanism is compounded as diabetic persons tend to have also higher levels of other risk factors, particularly obesity and hypertension, that continue to have an independent effect.[77] Not

surprisingly, cardiovascular events are the main cause of death in adult diabetic persons, with 80% of them attributable to CVD, 75% of which are CHD.[78]

However, there is still substantial uncertainty about the effects of controlling diabetes on cardiovascular risk. Epidemiological evidence suggests that diabetes it is an important, strong and independent risk factor. Yet, the results of randomized controlled trials on intensive glucose control strategies showed no effect on stroke outcomes or mortality, only a decrease in non-fatal myocardial infarctions.[79,80] This is interesting, as diabetes in considered to confer the same level of risk as those with established CHD[73], but this is probably because many diabetic patients when diagnosed already have advanced atherosclerotic disease.

The evidence for diabetes prevention appears rather different. A growing body of evidence based on randomized clinical trials suggest that diabetes incidence could be halved relatively quickly with multiple interventions including lifestyle and dietary changes.[81] Metformin has also been associated with a 31% reduction in the risk of diabetes in the Diabetes Prevention Program study, albeit smaller than the 58% risk reduction observed in the diet and lifestyle arm.[82]

These findings highlight the importance of preventing diabetes, thus focusing attention higher up in the causal web leading to diabetes and CHD outcomes.

3.2.6 Physical Activity

Physical inactivity has been recognized since the 1950s to be associated with total mortality and cardiovascular risk; however, most of the evidence base is observational. This body of evidence suggests reduction in total mortality and CVD risk of about 20-30%, often showing a graded response, and with benefits in other outcomes also, like diabetes, certain cancers and osteoporosis.[35]

Physical activity epidemiology is a difficult field, with controversies regarding exposure measurement and the complex causal pathways. However, most primary prevention guidelines recommend periods of moderate to intense physical activity as an effective intervention to reduce cardiovascular risk.[83]

3.2.7 Dietary patterns and other nutritional factors

I discussed above how some nutrients like salt or dietary fats are associated both with the levels of risk factors and with global CVD risk. Other dietary factors and diet patterns are also important.

There is substantial evidence to support the concept of cardio-protective nutrients and dietary patterns.[84] (These are summarised in Table 3-2)

A systematic review found strong evidence, by complying with most Bradford Hill criteria, for the beneficial effects of the intake of fruit and vegetables, nuts and "Mediterranean" or similar high-quality dietary patterns on CHD, confirming also the detrimental effects of trans-fatty acids and foods with high glycemic index. [85] The "Mediterranean diet pattern" and the DASH diet have shown beneficial effects confirmed in randomized controlled trial.[84] An analysis of diet patterns in the INTERHEART case control study has found that higher levels of a "prudent diet" (rich in fruits and vegetables) were inversely associated to the risk of a first acute myocardial infarction, across participants in 52 countries.[86] In general, dietary patterns are associated to high levels of cardiovascular protective individual nutrients and low content of detrimental factors.[84]

Among nutritional risk factors, industrial trans-fats merit special attention. These are artificial fats used mainly in processed food for commercial reasons and considered not to have any nutritional value. They have a profound effect on increasing CHD risk. Replacing 1% of energy from trans fat with unsaturated fats reduces CHD risk by approximately 12 % (5.5% to 18.5%).[48] Several countries have successfully implemented the complete removal of industrial trans fats from human food.[87]

In summary, certain dietary patterns have established cardio-metabolic benefits and are higher in dietary fibre, healthy fatty acids, vitamins, antioxidants, potassium, other minerals, and phytochemicals; and lower in refined carbohydrates, sugars, salt, saturated fatty acid (SFA), dietary cholesterol, and trans fat. The role of other dietary supplements, micronutrients and vitamins is complex and remains less than clear.[85]

Table 3-2 Evidence base for the association between diet and nutritional factors with cardiovascular disease

Nutrient	Intake Level and effect on CVD outcomes	Strongest Evidence Level*
Fruit	Increase, protective	Prospective observational studies on clinical endpoints
Vegetables	Increase, protective	Prospective observational studies on clinical endpoints
Whole Grains	Increase, protective	Prospective observational studies on clinical endpoints
Fish and shellfish	Increase, protective	RCT
Nuts	Increase, protective	Prospective observational studies on clinical endpoints
Dairy Products	Decrease, protective	Prospective observational studies on clinical endpoints
Vegetable Oils	Increase, protective	Prospective observational studies on clinical endpoints
Fats	Decrease, protective	RCT
Hydrogenated fats and oils	Decrease, protective	Prospective observational studies on clinical endpoints
Processed meats	Decrease, protective	Prospective observational studies on clinical endpoints
Sugar sweetened beverages and foods	Decrease, protective	Prospective observational studies on clinical endpoints
Alcohol	Decrease, protective	Prospective observational studies on clinical endpoints

*References available in Mozzafarian et al. [84]

3.2.8 Alcohol

The relationship between alcohol intake and CHD risk is complex. The relationship has been described as “J” shaped, with risk increased at high alcohol consumption or with no intake, and lower risk for low to moderate intake[88,89]; or as “L” shaped, where a protective effect was observed for alcohol consumption at low to high levels but not for no consumption.[90,91] There is greater clarity about increased levels of mortality with increasing alcohol consumption for stroke.[91-93]

A consumption of alcohol between 2.5 to 14.9 g/day was associated to a risk reduction of about 14% to 35% for cardiovascular disease mortality, and for incidence and mortality for CHD and strokes.[91,92]

The intake of ethanol seems to be the most important factor, rather than any specific components of the alcoholic beverage.[94,95]

However, the drinking pattern is more important. Regular, low to moderate intake seems to be protective[94-97], while episodic immoderate alcohol intake confers a considerable risk of incident MI and totally mortality.[96,98]

Furthermore, heavy alcohol intake might have mass consequences, as illustrated by the huge temporal variations in cardiovascular disease mortality rates seen in Russia and other ex socialist soviet republics after the breakdown of the union in the 1990s.[99] It is clear now that this phenomenon is not caused by misclassification of the causes of death.[100] Although causality has not been established with experimental data, current guidelines in most countries recognize that while low to moderate intake of alcohol CVD risk are beneficial, higher intakes are harmful. Alcohol consumption is thus not recommended by the British Heart Foundation, National Heart Forum or American Heart Association.[101]

3.3 OTHER RISK FACTORS: SOCIAL DETERMINANTS, LIFE COURSE INFLUENCES AND GENETIC FACTORS

3.3.1 Social determinants

The Socioeconomic determinants of health are usually assessed as social gradients in mortality or morbidity.

In the United Kingdom, these patterns are readily visible, with mortality gradients by socioeconomic levels or geographically across a North-South divide. For example, the mortality rate ratio between the most deprived quintile and the more affluent is 1.5 for both men and women, and almost 2 if we consider only those deaths happening under 75 years of age.[6] In the USA, persons without a high-school education lost almost three times more life years than more educated people, and cardiovascular diseases accounted for about 35% of this difference (coronary heart disease itself explained 11%).[102]

These gradients are also evident in the distribution of cardiovascular risk. For example, in the USA, there are major differences in risk factor prevalence and combined cardiovascular risk by ethnicity[103,104] and other measures of socioeconomic status.[105] In several European countries, persons in the lower socioeconomic strata are more frequently current smokers, have higher BMI, higher intake of alcohol and lower intake of fruit and vegetables.[106]

Worse childhood socioeconomic conditions are frequently associated with increased CVD risk in adulthood.[107,108] This is possibly mediated by early life and childhood trajectories in risk factors, predicting young adulthood cardiovascular risk factors levels.[11,109]

3.3.2 Life-Course influences

Social influences in childhood may also have an important effect on CVD risk in adulthood. The timing of other exposures starting intrautero -and even transgenerationally- are also important.[110] Perhaps the first evidence on early life influences on adult coronary heart disease risk was provided by Forsdahl, who found that early 20th century infant mortality rates were strongly correlated with CHD mortality rate seven decades later[111], suggesting that early childhood nutrition or perinatal phenomena might be linked to CHD risk.

The "developmental origins" of coronary heart disease hypothesis, as stated by Barker et al[112], suggest that many measures of foetal growth, as a proxy for the womb environment have shown that intrautero events are related to adult life CHD risk.[113,114]

Perinatal and early childhood influences also are linked to later , pre adulthood risk factor levels.[109,113] Moreover, cholesterol, body mass index, systolic blood pressure measured in childhood or adolescence predict CHD risk 50 year later.[113]

However, the scale of life-course effects on CHD causation remains unclear. Not least because such influences operating on individuals would be expected to operate, at the population level, as cohort effects.[115] However, the declining CHD epidemics in most high income countries can be explained better by period effects rather than cohort effects, (intriguingly, Singapore and Norway offer apparent exceptions).[116]

3.3.3 Genetic factors

Genetic factors play a causal role in coronary heart disease. The Framingham Offspring Study suggests that heritability may be an important factor for premature coronary heart disease. Participants with familial history of premature CHD (defined as history of CHD in first-degree relatives before age 55 in men and 65 in women), have twice the risk compared to those who not, even adjusted for classical risk factors.[117] Single gene association and several candidate loci and gene sets has been identified in linkage and genome-wide association studies, usually associated with metabolic pathways related to lipid metabolism.[118]

However, in general, the potential candidates have small effect sizes[119], low predictive power and low population impact measures[119] compared to classical risk factors.[120]

The rapid changes over time within countries and the marked differences in CHD mortality observed between countries , as discussed in chapter 2, (all of which I will further discuss later), powerfully indicate a major role of environmental factors and make very implausible to attribute such trends to changes in the distribution of genetic determinants.[121] Moreover, the classical studies of migrants, particularly among Japanese populations, suggested that the risk of CHD and stroke increase substantially when exposed to Western dietary environments.[122,123]

The interaction of environmental factors with particular genetic risk profiles may also be important in CHD. Thus, for example, APOe e4 high risk alleles might not affect CHD risk in absence of smoking .[124] Although Mendelian genetics or even genome wide association studies fail to explain a substantial proportion of the burden of coronary heart disease, heritable and non-heritable epigenetic changes might occasionally play an important role in individual cases.[125]

3.4 "TRIGGERS"

An often neglected issue when discussing coronary heart disease incidence is the concept of "triggers". Triggers are exposures that will precipitate clinical events in persons who already have developed atherosclerosis. Although not strictly causal factors of atherosclerosis, they are important in determining short-term temporal patterns of incidence rates, measured as the occurrence of clinical events including death.

Several factors have been proposed as potential triggers for the acute forms of CHD, like air pollution, traffic exposure, alcohol consumption (binge drinking pattern), cocaine use or infections, sudden stress, and extreme exertion. For some of them, the case for biological plausibility is solid.[126] However most of the evidence came from observational studies (time series), so there is still potential for significant confounding effects and biases.

Triggers also are described of having a "harvester effect".[127] Triggers essentially precipitate events that will occur anyway in a few hours, days or weeks, by depleting the high-risk pool of individuals.

In any population, the incidence rate is the weighted average of the high-risk pool and the low-risk pool of individuals. When the population is exposed to the trigger, the most vulnerable will have events at a higher rate, creating a "spike" of mortality.

However, as the high-risk pool is depleted, the low-risk pool make a larger contribution to the incidence rate, resulting in lower than average rates for a period. Finally, as the high-risk pool recovers, the incidence rate returned to its usual levels.

Nevertheless, triggers offer a potentially interesting explanation in terms of mass exposures that can have a noticeable effect on event trends. For example, the population attributable fractions for several trigger candidates have ranged from 1% (cocaine and marijuana use) to 7% (air pollution or traffic exposure).[128]

Some of these triggers might also have long-term effects, and perhaps at this point, they might be better considered alongside the mayor risk factors discussed previously. For example, cohorts studies exploring the risk associated to particulate air pollution have found a 10% increase in all cause mortality per 10 ug/m3 in long term average exposure (follow-up times ranging from 2 to 30 years).[129] Risk related specifically to CVD appears to be similar [129] and are the major component of the increase in total mortality. However, potential for substantial residual confounding exists, as these studies did not control extensively for other disease risk factors.

3.5 EVIDENCE FOR STROKE

The term cardiovascular disease comprises a range of diseases, including coronary heart disease, stroke and peripheral vascular disease. Although a very heterogeneous category, the ischemic forms of cardiovascular disease are the predominant ones and share most of their determinants. My emphasis on CHD is therefore hopefully justifiable since in the majority of countries it is the most important disease of this group in terms of burden of disease.

However, some differences exist within the umbrella term cardiovascular disease. I will therefore briefly consider stroke, as an example of another disease included with the CVD category.

Stroke is a heterogeneous disease, but is mainly composed of ischemic and hypertension related hemorrhagic strokes. However, the main burden is related to ischemic, which comprise about 80% of the disease burden.[130]

Most of the risk factors for coronary heart disease are also risk factors for stroke, but the strength of the association is different. If we consider total stroke, hypertension is significantly more important for stroke than for CHD (PARF 35% vs. 18%) as well as the ratio of Apo B/A1 (PARF25% vs. 49%).[131]

As I discussed before, heavy alcohol intake increases the risk of stroke, although there is still a more complex effect on CHD outcomes.

Certain heart conditions are specific risk factors for stroke, like atrial fibrillation or dilated cardiomyopathy. Both conditions increase the risk of cerebral embolism, a cause of ischemic stroke. Risk factor for stroke have been found to be independently associated to stroke in high income and low income countries participating in the INTERSTROKE study.[132]

3.6 THE EFFECT OF THE MAJOR RISK FACTORS IS UNIVERSAL

This is an important question when trying to understand trend determinants globally. The assumption usually made is that they are universal, e.g. that the direction and size of the risk factor effects is similar across populations.

The studies trying to replicate the Framingham findings consistently showed that the classical risk factor levels are useful to grade risk in Western and non Western populations, although calibration is an issue across different populations.[10,133] The international case control study INTERHEART, and the prospective studies collaboration and Asia Pacific collaboration have also suggested that the risk conferred by the classical risk factor is similar across Western and non Western populations.[25-27,56]

However, Countries like France or Japan show low CHD mortality rates with relatively high levels of risk factors. This situation, often described as “the French Paradox” or the “Japanese Paradox”, might jeopardize the idea of “universality of risk factors effects”. However, these

paradoxes have been variously explained in terms of mortality misclassification the existence of additional protective risk factors, or by lag times which have been ignored.[13,134]

The vast amount of data showing the association of risk factors with cardiovascular outcomes in many countries, populations and different time periods suggest that assuming that risk factor effects are essentially universal is based on solid grounds.

3.7 THE MAJOR RISK FACTORS EXPLAIN MOST OF THE OCCURRENCE OF CORONARY HEART DISEASE

As I have discussed, the evidence base for establishing the causation of cardiovascular diseases is broad and deep, solidly based on a combination of biological, observational and interventional evidence that mostly fulfil Bradford Hill criteria. However, the list of confirmed and potential risk factors for CHD and stroke exceed that of the "classical" ones. Candidates are thrombotic and inflammatory biomarkers, lipid sub-fractions and endothelial function measures. A huge body of literature and current research is focused in finding novel risk factors for CHD.

This quest has been fuelled by the claim that only half of CHD incidence can be explained by the classical, major biological risk factors, promoting a frantic search for new ones. However the source of this statement is difficult to locate, as discussed by Magnus & Beaglehole in a key paper in 2002.[135]

The debate is essentially about finding new targets for intervention. For this reason, it is easier to claim the importance of the candidate novel risk factors based on relative risks. A better way to understand the impact of a risk factor can be summarized as the population attributable risk fraction (PARF), a variable that reflects both the risk factor frequency in the population and the strength of its association with CHD. One of the crucial assumptions of this concept is that the risk factor should be causally related to the outcome, because the PARF estimates the proportion of disease incidence that can be eliminated if the risk factor is completely removed from the population. For example, a weak risk factor but very prevalent will have a bigger impact compared to a stronger, but less common.

By using the PARF approach, the INTERHEART study estimated the population attributable fractions associated to lifestyle and diet related risk factors is about 90%, suggesting that there is little room for significant "novel" candidates, whatever strength they might have.

From another perspective, a similar conclusion can be reached by examining the incidence of CHD in people at "low risk " for CHD, defined in terms of people that never smoked and have no diabetes, normal or low blood pressure and blood lipids.[136,137] This group experienced extremely low cardiovascular disease rates.

Another important distinction is to differentiate causal risk factors from the simple identification of earlier, preclinical phases of an already established pathological process. The distinction between a risk factor and a risk marker is thus important, mainly because some disease control strategy involves the identification of individual with subclinical disease.

Describing the risk factors in terms of their prevalence and the strength of their association with CHD is then of paramount importance for public health.

The place of a risk factor in a complex causal network is also important. Many risk factors distal to outcomes make them desirable intervention targets, as they will have downstream effects on more proximal risk factors. Therefore, it is perhaps better to talk about "Major causal pathways" to reflect better the complex web of causation of coronary heart disease (Figure 3 – 1).

3.8 RECENT TRENDS IN CARDIOVASCULAR RISK FACTORS

Global recent trends in risk factors showed a complex picture.

The Global Burden of Disease has completed global regional and national estimates of trends between 1980 and 2008 for systolic blood pressure, cholesterol, obesity and diabetes, using the best data available and then conducting statistical multilevel modelling for inputting missing data on countries or years, "borrowing" information from neighbouring countries, regional estimates or information from previous trends.[64,138,139]

BMI globally demonstrated increases about 0.4 kg/m2 per decade in men, and 0.5 kg/m2 per decade in women. The largest increases were observed in Oceania, but Western high-income

countries are amongst the countries with most marked increases. In contrast, countries in central and eastern Europe, Central Africa and South Asia showed predominantly flat trends.[138]

Diabetes is increasing globally, in parallel with the increase in obesity seen almost worldwide. This increase is particularly important in low and middle-income countries.[140] The Global Burden of Disease Study estimated that age-standardised adult diabetes prevalence was 9·8% (8·6—11·2) in men and 9·2% (8·0—10·5) in women in 2008, up from 8·3% (6·5—10·4) and 7·5% (5·8—9·6) in 1980. The increase was more marked in the USA compared to Western Europe.[141]

SBP decreased globally by about 0.8 mmHg per decade in men and 1 mmHg per decade in women, with the largest decreases in Australasia, North America and Western Europe. However, countries in East Africa, Oceania and South and East Asia showed clear increases.[64]

Cholesterol change very little globally over that period, falling less than 0.1 mmol/l per decade. This reflected conflicting trends, which cancelled out. Whereas cholesterol levels fell in Australasia, North America and Western, Central and Eastern Europe, they increased in East Asia, South East Asia and Oceania.[139]

Smoking is decreasing in men in many countries, although often very slowly. In the USA, during 1998-2008, the proportion of U.S. adults who were current cigarette smokers declined 3.5% (from 24.1% to 20.6%).[142] The UK also showed significant declines, however, in young adults, that decrease is slow or even stopped.[6]

Smoking prevalence rates for most countries, but particularly for non-Western, low and middle income countries are still very high in men, and in women are often increasing from historically low levels. [143]

3.9 THE RISK FACTOR PARADIGM AND THE CONTROL OF CORONARY HEART DISEASE BURDEN

There are many possible strategies to tackle the high impact of cardiovascular disease and in particular coronary heart disease. The main goal of these strategies is to decrease case fatality, reduce incidence and to improve quality of life and function.

3.9.1 Reducing case fatality rate, recurrence and improving functioning

The explosion in the 1980s and in the 1990s of the availability of effective interventions to decrease CHD mortality and morbidity has been certainly one of the successes of Medicine in the 20th century, and helped to establish the evidence based medicine paradigm.

Treatments reduce dramatically the case fatality rates in high-risk situations like the acute coronary syndromes. The development of coronary care units, techniques aimed to unblock acutely occluded coronary arteries and the use of antithrombotic agents can together reduce case fatality rates by almost a third.[144]

These treatments have not only reduce mortality acutely, and thus usually resulted in smaller infarct sizes, resulting in medium and long term benefits leading to a decrease in post-ischemic heart failure.[145,146]

Major reductions are achievable by reducing case fatality rates in groups with larger numbers of patients or with the highest mortality risk. The treatment of the large and increasing pool of survivors of myocardial infarction and those who underwent coronary revascularization can reduce mortality substantially.[144] The current strategies include the use of aspirin, statins, angiotensin converting enzyme inhibitors and rehabilitation.

Patients admitted to hospital with heart failure experience a high mortality rate (about 50% at within 2 years), a mortality comparable with some common cancers.[147] However the use of aspirin, angiotensin-converting enzyme inhibitors and spironolactone offered a substantial risk reduction of about 30%.[144]

Although revascularization strategies are widely used and undoubtedly benefit individual patients, their contribution to population-wide mortality reduction is small.[144,148,149] Moreover, only coronary artery bypass surgery [CABG] have shown definite mortality reduction effects, while percutaneous coronary interventions (PCI) for revascularization in chronic angina has been proven not to be superior to adequate medical therapy.[150]

Rehabilitation in CHD, both after acute myocardial infarction[151] and in chronic settings [151,152] showed a reduction of 20-30% in mortality, although in part the effect could be attributed to better use of other secondary prevention treatments and risk factor reductions.[153]

In modelling studies, the contribution of evidence-based treatments to the reduction in CHD mortality in many Western countries has ranged from 45 to 50% in the period 1980-2005.[144,148,149]

3.9.2 Reducing CHD incidence

Because of the comprehensive knowledge that has developed over the last 4 to 5 decades regarding CHD causation, reducing the risk of developing coronary heart disease in the first place is a primary goal to control disease burden. Prevention is important, since the reduction in case fatality rates achievable with evidence based therapies, still fail to substantially reduce the overall disease burden, as many people surviving myocardial infarction or living with heart failure has marked declines in their quality of life[154] and consume a large proportion of health care resources.[6]

Prevention will decrease the overall burden by not only decreasing mortality rates but also by prolonging the extent of life lived without disability.

Two critical questions currently dominate the debate on prevention of cardiovascular disease: At which level of risk preventative interventions should be undertaken and at what age should it start?

Prevention can be targeted at the individual level, by identifying those at high risk of coronary heart disease based on their age and the presence of risk factors. An assessment of the overall cardiovascular risk for an individual can be measured using risk functions. These are usually regression equations derived and validated in cohort studies, exploring the association of the major risk factors with CHD events and mortality. Examples include the Framingham Risk Score, the EUROSCORE and Q RISK.[155-157]

Once identified, these “high risk individuals” are selectively targeted to receive smoking cessation therapies, diet and physical activity advice, and specific medications, including anti-hypertensive drugs and statins in certain situations.

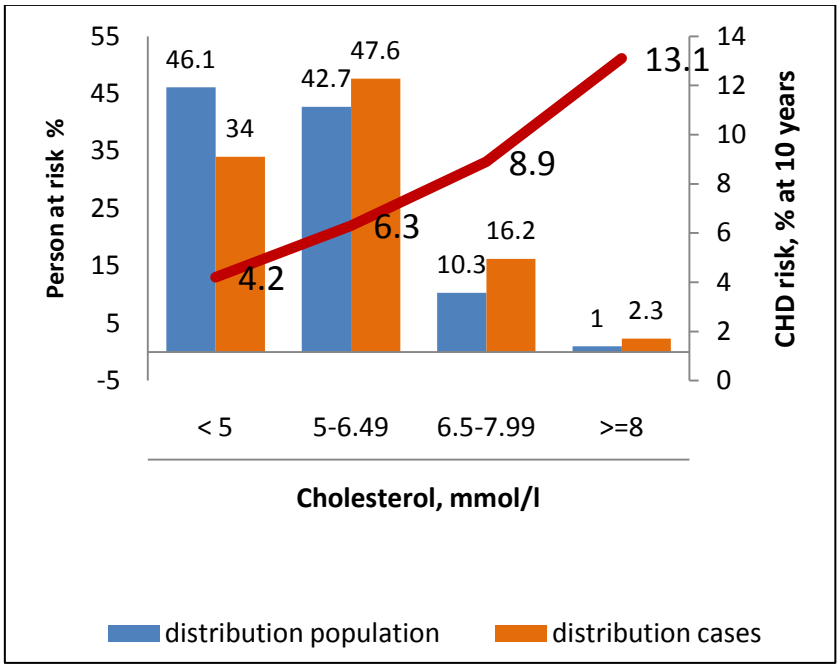
Although individual therapies have shown beneficial effects in high-risk individuals with hypertension or elevated lipids[24,158], randomized clinical trials of multiple risk factor interventions have frequently shown disappointing results. Most programmes targeted at cardiovascular disease free participants failed to show reductions in events or mortality, or sustained improvements in the levels of risk factors.[159]

Another important limitation of these approach is the ability of the risk functions to adequately identify individuals at risk.[160] Among Individuals classified at "high-risk" levels, an unacceptably large proportion of them may still not experience events. [161] Moreover, substantial residual risk might exist when only controlling risk factors levels with drugs, as generally the risk reduction achievable with successful blood pressure reduction or statins in primary prevention settings range from 15% to 25%.[162,163] These strategies require substantial resource investments from the Health Services, and require patient compliance over the long term, and susceptible to the inverse care law.[164] Is not surprising then that targeted intervention might result in an increase in socioeconomic inequalities.[165]

The alternative approach is to attempt to reduce risk factor levels by shifting its distribution to lower levels across the entire population, a strategy championed by Geoffrey Rose.[166]

This concept is based in the observation made originally by Wilhelmsen et al [167] that most cardiovascular events and deaths occur in individuals possessing risk factors levels near the population mean, and fewer events come from the relatively small numbers of individuals with high risk factor levels and corresponding much higher relative risks. This observation has been widely replicated, including in the British Regional Heart Study[168], in Spain[169] and in the Netherlands. (Monique Verschuren, personal communication)(Figure 3-2)

Figure 3-2 Distribution of CHD risk, cases and cholesterol levels in the Dutch population (Verschuren M, personal communication)



The potential for reducing events by shifting the risk factor distribution is therefore substantial. Emberson et al have looked at the potential gains for a shift in risk factor distribution of blood pressure, blood cholesterol or both as compared to only treating English persons with high levels of these risk factors, based on current guidelines.[168] They found that if 6% of the population who is at ≥30% total CVD risk at 10 years is treated, a reduction of 11% could be achieved. Decreasing the threshold to ≥ 20%, it could reduce events by 34%, treating 26% of the population. A reduction of 10% in cholesterol and blood pressure, relatively modest, could achieve a 45% reduction in events. However, an analysis by Manuel et al[170] considered that the benefits from targeted strategies are higher than those achievable with the population approaches, in the Canadian population. They focused on cholesterol, and they found that targeting high-risk individuals would avoid 290 deaths per 100,000, while a population-wide, modest reduction in cholesterol will result in 42 per 100 000 fewer deaths. However, they modelled only a 2% reduction in population cholesterol levels, an extremely conservative goal. Far greater declines have been observed in Mauritius (15%) [171], and in North Karelia and Kuopio, Finland (about 18%).[172]

Shifting the population distribution of risk factors involves reducing mass exposure to risk factors or its determinants. For instance , governmental and Food Standards Agency actions in the UK resulted in a decline in salt consumption from 9.5 grams per day in 2000 to 8.6 grams per day in 2008[173]. The US, Japan, Australia, Canada and Ireland achieved similar population wide reductions in salt intake.[58] Furthermore, following the North Karelia project, Finland managed to substantially reduce population means of cholesterol and salt over a 30 years period.[172,174] Similar progress have been achieved with tobacco legislation and taxation[175], and by banning trans-fats.[87]

Population level interventions, when correctly implemented, also have less potential to increase inequalities[165], because they are not dependent on individual choice of more healthy or less risky behaviours. Population interventions are usually cost-saving and thus represent particularly good choices for resource-poor countries.[176,177]

In terms of policy, the two options can be cost effective, even in low and middle-income countries, and probably complementary[176,178], when resources are available. But in severely limited resource settings, population level interventions will probably incur in less direct costs and investment.[178]

The polypill concept exploited the notion of achieving big reductions in disease burden by reducing risk in large subsets of the population at average risk. This concept, first introduced by Law et al in 2003[179], consists in incorporating in a single tablet or capsule a combination of drugs to

reduce several cardiovascular risk factors simultaneously, each component with demonstrated efficacy in reducing risk factor levels and cardiovascular fatal and non fatal events in randomized clinical trials. The concept has now been tested in clinical trials. Maleksadeh et al [180] found reductions in blood pressure and lipid levels, but with large attrition rates, with similar findings in the larger Indian Polycap study.[181] However, none of these trials has looked at clinically important outcomes and both have a short duration [under a year]. Although these results are promising, the polypill strategy is still heavily dependent on choices made by practitioners and patients, and since its scalability is problematic, this may preclude its ability to reduce the burden of cardiovascular disease compared to population level interventions.

3.9.3 Early start for preventative interventions

The development of atherosclerosis is a long process, starting in the womb and ending with fatal vascular events. Multiple disease control strategies can be employed at different points in this timeline, but their potential to decrease morbidity and mortality necessary decrease as soon as the disease is clinically apparent. Preventative strategies thus have the biggest potential the earlier they are implemented, delaying or preventing the development of dangerously high levels of proximal risk factors in young adulthood.

The concept of **cardiovascular disease primordial prevention**, pioneered by Strasser[182] and championed by Labarthe[183], is perhaps the earliest possible strategy to implement. Essentially, primordial prevention refers to strategies that preclude the development of adverse risk factor levels in the first place. However, this concept has not been widely adopted until recently, partly because now we have more evidence about the important of life course influences and early age risk factors trajectories as determinants of later life cardiovascular risk.

3.10 CONCLUSIONS

The causality of coronary heart disease has been comprehensively studied over the last five decades. The relationship of cardiovascular disease occurrence (mainly coronary heart disease and stroke) with diet, smoking and other lifestyle factors is now well established. The role of biological, downstream risk factors and their link with more upstream determinants has also been established with increasing confidence. As a result, many potential targets for intervention exist and now form the basis for modern cardiovascular disease prevention strategies. Furthermore, when deciding

actions to control the future disease burden, searching for new risk factors might be considered an activity of secondary importance

The current paradigm in disease causation usually assumes that the development of clinical cardiovascular disease takes decades, as the atherosclerotic plaque slowly build-ups until it reaches a critical point when sudden occlusion (often the result of thrombotic and inflammatory changes in the plaque environment) leads to clinical events, including death.

A corollary of this reasoning is that prevention might also take decades to reverse these processes, before showing any benefits. The timescales for change and the speed of change after any intervention are therefore of crucial importance from a public health perspective. Any public health strategy, either individual high-risk targeting or the population wide approach, might then be expected to deliver its benefits only over the long term. That concept will be further scrutinised later in this thesis.

This knowledge of CHD aetiology has been developed while the Western world experienced a marked decline in cardiovascular disease mortality. This much acclaimed decline attracted a lot of attention, particularly in identifying the drivers of these changes. This story is one of success and is very much celebrated. It has helped to understand and to refine the causal paradigm of cardiovascular disease and to drive attention to monitoring mortality trends as a measure of our understanding of the efficacy of interventions aimed to control disease burden.

In the next chapter, I will review our existing knowledge regarding coronary heart disease mortality trends, and discuss their possible underlying drivers.

4 CURRENT TRENDS IN CHD MORTALITY: DETERMINANTS AND SPEED OF CHANGE

4.1 INTRODUCTION

Perhaps one of the most interesting epidemiological phenomena was the massive decline in CHD mortality observed in Western countries occurring since the 1960s. This is reflected in many opening sentences in cardiology research papers and textbooks, probably second only to the other statement emphasising the enormity of the CHD as a public health problem.

In CHD epidemiology, the important question about to what are the drivers of the decline in CHD mortality has been asked in a meeting of the National Heart, Lung and Blood Institute held at Bethesda, USA in 1978.[184] This conference debated extensively the contribution of changes in incidence (as a proxy of a change in disease determinants) or in case fatality (suggesting the effect of medical treatments) as explanations for the decline in CHD mortality.

Although is assumed that incidence is the most appropriate outcome measure to use when looking for answers to the question asked by the Bethesda Conference, measuring it at the population level is a difficult task and only few studies have managed to achieve this.

Many studies relied on coronary heart disease mortality. Although not an absolute correlate of incidence, CHD mortality rates has been considered as a good proxies for it, particularly since our knowledge of risk factor effects and the impact of medical treatments on population mortality and case fatality rates has been better understood.[144] Moreover, is easier to measure than incidence, allowing examining trends over longer period of time using readily available data.

Although mortality coding and changing definitions might add noise to these trends, the quality of its registration and coding has been substantially improved, particularly in the most recent decades and in high-income countries.[185]

4.2 ANALYZING AGE-ADJUSTED AND AGE-SPECIFIC TRENDS

Classically, CHD mortality trends are analysed adjusting them for age, to remove the confounding effects of ageing (a risk factor that cannot be modified) and thus make the trend a better reflection of those other disease determinants that might be more responsive to intervention.

However, much emphasis has been put on age adjusted rates as oppose to age specific ones, and also little attention has been paid to direction and pace of change, probably because the analysis has mostly focused on Western populations experiencing constant declines since the 1970s. The Russian mortality crisis [99], studies on Chinese CHD trends [186] and central European CHD mortality trends[187] showed that decline is not necessarily a universal phenomenon.

I have discussed that some risk factors are showing adverse increasing trends, particularly diabetes and obesity, while in some countries and particularly in the young, risk factors like smoking and systolic blood pressure are declining at a lower rate in recent years.

Age, cohort and period effects are important considerations, since they might offer insights on changing exposures. Rose suggested that cohort effects are possible in connection to the Barker Hypothesis on early life origins of CHD (See chapter 3)[188], or perhaps by later in life to cohort-specific exposures. Moreover, Wilson et al suggested that recent cohort effects in young people can't be excluded for young adults in an analysis of Australian CHD mortality up to 1992[189]. However, is difficult to find any other evidence of cohorts effects.[116] The only exceptions are Singapore[190] and Norway where the decline started earlier in younger cohorts.[191] However, these papers looked at the periods around the peak of incidence of the epidemic (1970s-1980s). If these analysis are extended further in time, the evidence for cohorts effects disappear.[116]

More recently, adverse age-specific effects have been identified. Ford et al [192] recently described a flattening in CHD mortality in the US population, particularly in young adults, starting in 2000, although based only in a couple of years of data. This is consistent with adverse risk factors trends in the younger age groups and is therefore of concern.

The use of age-adjusted rate might conceal important age and gender specific trends that could shed light on ongoing changes in trends in disease determinants, highlighting the importance to observe in more detail those age specific effects.

4.3 TEMPORAL EVOLUTION OF THE CHD EPIDEMIC

Geoffrey Rose developed the idea that the CHD epidemic is essentially the same epidemic in all countries [188], sharing the same determinants but happening at different times. It is possible then to describe CHD epidemics in terms of waxing and waning "rates increase" and "rates decline" phases.

This concept can be better understood by considering the peak year of the epidemic as the starting point for the decline phase of the epidemic in a given country or defined population. The decline of CHD mortality in the US started earlier in California, Maryland and the District of Columbia (towards 1960) than in the southeast states, were the decline started later (towards 1965).[193] In most Western countries the CHD epidemic peaked during the 1970-1980s and then entered the decline phase whereas Central European countries, peaked later (1990s) and since then has shown dramatic declines. Some countries, particularly China and some former Soviet Socialist Republics still are in the "increase phase", while low income and middle-income economies only experienced this recently. Some countries however, are in a "plateau" phase, were rates change little.[194]

The pace of change can also be different, even in countries in the same phase of the epidemic. For example, Ireland showed faster rates of decline than the UK or Finland in the period 1985–2006.[195] Interestingly, risk factors contributions to the observed trend also varied across countries experiencing the same phase of the epidemic. For example, changes in risk factors exposure contributed the most to the observed decline in mortality in the Scandinavian countries (about 70%)[148,196] while in the UK and USA the contributions of risk factors and treatments were more balanced.[144,149]

The value of studying trends in mortality thus resides in not only estimating the temporal evolution of coronary heart disease burden, but also in gaining insights on what is driving the epidemics in a specific population.

4.4 WHAT DRIVES THE TRENDS? INSIGHTS FROM OBSERVATIONAL AND MODELLING STUDIES

Framingham is the paradigmatic study describing the relationship of the major risk factors to CHD incidence, and the Seven Countries Study showed that they are important in a range of populations, finding recently confirmed by the Asia Pacific Cohorts, the Prospective Studies Collaboration and the INTERHEART study.

However not many studies have addressed the question of what drives these trend as raised by the Bethesda conference. Because this question cannot be practically addressed with randomized controlled trials, it has been mainly studied using observational designs and more recently, modelling studies.

I will describe some of the major studies that provided evidence to explain what drives CHD mortality trends. One of them is the MONICA, a large international observational study and two modelling studies, the US CHD Policy model and the IMPACT model. Finally, I will discuss Finland, a country where both observational and modelling evidence is available.

The MONICA Study[20]:

Together with the Seven Countries Study and the Framingham Study, the MONICA Project (Multinational MONItoring of trends and determinants in CArdiovascular disease) helped to establish our current understanding of the epidemiology and control of cardiovascular disease. MONICA objectives were first to observe the trends in CVD mortality and morbidity and second to evaluate the extent to which these trends were related to changes in known risk factors, including daily living habits, health care, and major socioeconomic features. The study was conducted in 38 populations in 21 different countries starting in 1980 and finalizing data collection by the late 1990s. They assessed the contribution of risk factors to CHD incidence rates by looking at the association between 10 year trends in major risk factors (smoking, blood pressure and blood cholesterol) and 10 years trends in incidence (fatal and non fatal events). Careful biochemical measurements and strict event ascertainment and death certification procedures were key features of this exemplar study. They monitored almost 13 million people over 10 years, and more than 300,000 men and women were sampled and examined for risk factors. During the 10 year period they registered 166,000 myocardial infarctions.

In the MONICA populations, CHD mortality rates fell 4% per year. About two thirds of the observed fall could be attributed to the fall in event rates, while one third could be attributed to a fall in case fatality[20]. However, they were unable to precisely quantify how much of these falls could be attributed to changes in risk factors[18] or to evidence based treatments.[19] The effect of individual risk factors on risk was lower than the observed in the cohort studies. In part, this can be attributed that to some extent, the analysis in the MONICA study are at the ecological level, and that they were not corrected for dilution regression bias. When the association in cohort studies is explored without taking into account this bias, the results are similar.[148,197]

US CHD Policy Model[198]

The US CHD Policy model is a state-transition, cell based model developed in the1980s.[198] It was initially used to examine trends in CHD mortality[199,200] and expected gains in life expectancy from risk factor modifications.[201] This model was also used to evaluate the cost-effectiveness of specific medical interventions for primary and secondary prevention of CHD[202-204], salt reduction policies[205] and health promotion activities.[206]. The model showed that in the US population and for the period 1980-1990 risk factor changes contributed 50% to the mortality decline while treatments contributed 43%.

IMPACT

IMPACT is a cell-based model originally developed by Capewell and colleagues in 1996.[5] Using a MS EXCEL spreadsheet, this model combines data from many sources on patient numbers, treatment uptake, treatment effectiveness, risk factor trends and consequent mortality effects. The deaths prevented or postponed (DPPs) over a specified period are then estimated. The model can be used to estimate the proportion of change in mortality attributable to specific treatments or risk factor changes. It can also estimate the future consequences of altering treatment strategies and changing population risk. The model also estimates life years gained and cost-effectiveness for specific interventions.

IMPACT, an ongoing project, has been used to explore the contributions of risk factors and treatments in over 10 countries. In most of the studied countries (New Zealand, Scotland, England & Wales, Sweden, Italy, Spain, Iceland, USA and Canada) CHD mortality rates has been declining. The IMPACT model consistently found that about 40 to 72% of the fall in deaths could be attributed to risk factors changes and 23 to 55% to treatments.[144] An interesting observation from IMPACT modelling related to the City of Beijing, were CHD trends were increasing, essentially driven by a

huge increase in cholesterol levels. This might be related to the rapid adoption of a "Westernized" diet, rich in saturated fats.[186]

Particularly interesting are the recent findings in central European populations, were rapid declines in mortality has been observed after decades of increasing rates and linked to profound socio-economic changes resulting in substantial modification of the exposure to CHD risk factors. I will describe in chapter 6 an analysis using the IMPACT model of the trend determinants for one of the most interesting countries in the region, Poland, which experienced a dramatic decline in CHD mortality since the 90s. I will also use the IMPACT model to study recent English trends by socioeconomic status (chapter 7) Methodological details of the model will be presented in the relevant sections and in appendices 2 and 4.

Finland: Observational and modelling studies

Finland experienced a marked decline in CHD mortality during the 20th century, associated with the implementation of nationwide, population level policies. Trends in mortality and in the major risk factors were then closely monitored. Thus detailed analysis of the period of sustained declined between 1972-2006 is available.[207]

Serum cholesterol declined significantly in both men and women over that period. Blood pressure declined up to 2002, but levelled afterward. Smoking followed a more complex pattern, declining in men but increasing in women until 2002, and levelling off since then. BMI increase in men throughout the period and in women started to increase in 1982.

Collectively, the changes in risk factors explained about 60% of the 80% observed decline in CHD mortality.

The Finnish IMPACT model[148] found similar contributions of risk factors to that observed by Vartianen et al. In this modelling exercise, risk factors explained 48 to72% of the observed fall in coronary heart disease mortality between 1982-1997, while medical treatments explained 23%, consistent with the observational data.[148]

4.5 CONCLUSIONS

Although still there is not a definitive answer to the question posed at the Bethesda conference, insights coming from observational and modelling studies suggest that both risk factors and medical treatments contributed substantially to the observed trends in CHD mortality.

The fact that the current epidemics across the globe are at different stages and that rates are increasing in many countries makes current study of these trends pertinent, especially given the alarming increases in obesity and diabetes.

However, the current emphasis on monitoring trends using age-adjusted rates might present an incomplete picture of the state of the epidemic in individual countries, because this might conceal important differences in age-specific patterns that might mark the beginning of a new phase in the CHD epidemic.

The decades long decline in age adjusted trends in the Western world convey the idea that trends are invariably longstanding, almost set in stone. In the next chapter, I will challenge this cosy concept, by studying recent changes in the pattern of the CHD epidemic in a variety of Western countries.

5 STUDIES ON RECENT TRENDS IN CORONARY HEART DISEASE MORTALITY RATES: ENGLAND & WALES, AUSTRALIA AND THE NETHERLANDS

5.1 INTRODUCTION

Most of our knowledge about the temporal evolution of the CHD epidemic was obtained from age-adjusted analysis of the CHD mortality rate. As discussed in chapter 4, emerging age-specific patterns are suggestive that this decline may not necessarily last forever. Detailed analysis of the temporal evolution of the rate of change of trends has been usually overlooked, or merely described as a relative change over a period and therefore assumed to be linear. However, trends can be more complex, and identifying periods where the trend change at a different speed might help us to better understand the underlying drivers.

In the following section, I will discuss the main methodological approach used in analyzing temporal dynamics of CHD mortality trends. I will then use this method to study recent trends in England & Wales, Australia and the Netherlands. In the following chapters, I will examine trends in Poland, Scotland and England, focusing on the underlying determinants (drivers).

5.2 METHODS: TREND ANALYSIS USING JOINPOINT REGRESSION

This section describes the approaches I used for the trend analyses presented in this thesis. Details on specific issues relevant to each setting will be described in the methods section of each analysis.

The key question to answer is whether the rate of change varies in different time periods.

Most of the descriptive analyses on CHD trends have relied on simple qualitative trend descriptions. However, more formal trend analysis have rarely been done, except in the field of environmental CHD epidemiology[129]. Regression methods have been used to explain trends in terms

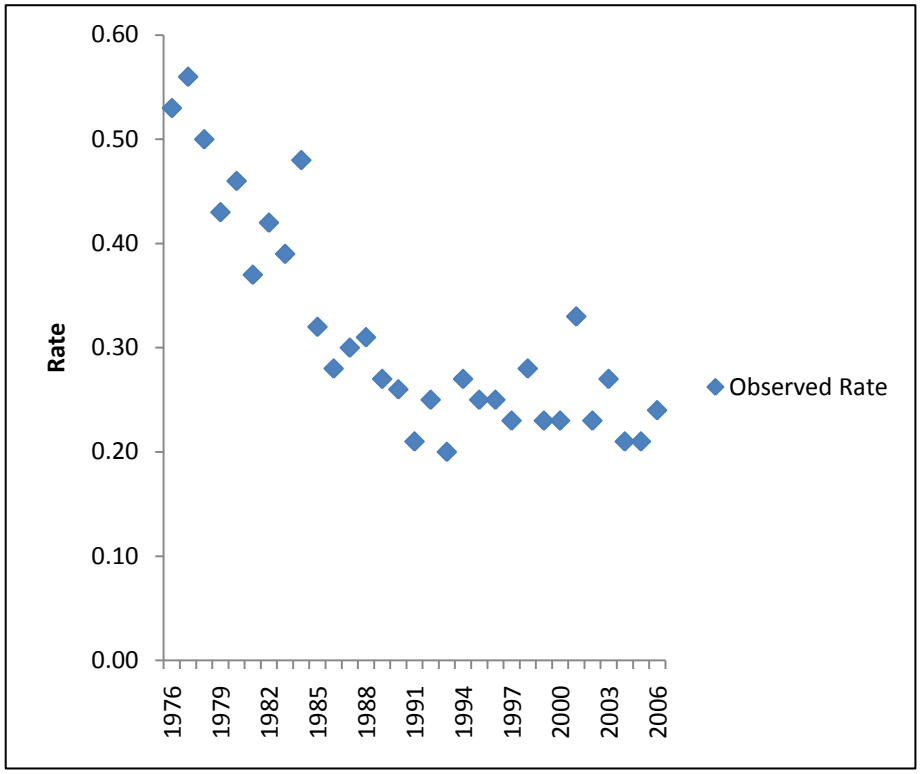
of risk factor contributions[18]; but the question of direction and speed of change in CHD epidemiology has not been formally addressed. In part, this can be attributable to the slow adoption of ***change-point methods*** in cardiovascular epidemiology. This type of time series analysis look at trends trying to identify points where the trend change and is commonly used in fields like cancer epidemiology, econometrics and statistical process control.[208]

One of these methods is the Joinpoint Regression Analysis approach. This was developed by the U.S. National Cancer Institute with the purpose of describing change in cancer rates in terms of pace of change, direction of that change and statistical significance.[209]

Joinpoint regression models explore the trend data to find points in time ("joinpoints") defining segments where the trend has a constant pace of change. The method starts by assuming that there are no "joinpoints" thus, the entire trend has the same rate of change. Then, it iteratively adds joinpoints by performing a "grid search" (looking for points in time that minimize the error on the change of the rate) and thus identifying the years where the trend rate of change might vary, effectively identifying the "joinpoints". Then, it formally tests whether these additional joinpoint creates segments with different rate of change. Statistical significance is tested using a Montecarlo permutation method. Permutation test method and the Bayesian Information criterion method offer two alternative goodness of fit approaches to select the optimal number of joinpoints. The Permutation test approach uses a sequence of permutation tests to select the number of joinpoint and controls the error probability of selecting the wrong model at a certain level (i.e. 0.05) using the Bonferroni multiple comparisons adjustment. The Bayesian Information criterion method (BIC) approach finds the model with the best fit by penalizing the cost of extra parameters, favouring trends with fewer segments. The models selected by BIC tend to fit the data well but are less parsimonious. The PT approach has worked well for cancer incidence and mortality data, however little experience is available in the cardiovascular literature, although the results of both approaches are generally concordant (see appendix A1). Information of the uncertainty around the rate of change and the time of the point of change in the trend can also be obtained.

Identifying patterns in a trend is thus the main goal of the approach. Figure 5-1 and 5-2 illustrate an example of this analysis. Figure 5-1 shows a rate plotted over time. The trend appears complex, with a period of decline that seems to have changed around 1988, continuing a slow decline or even a flat pattern.

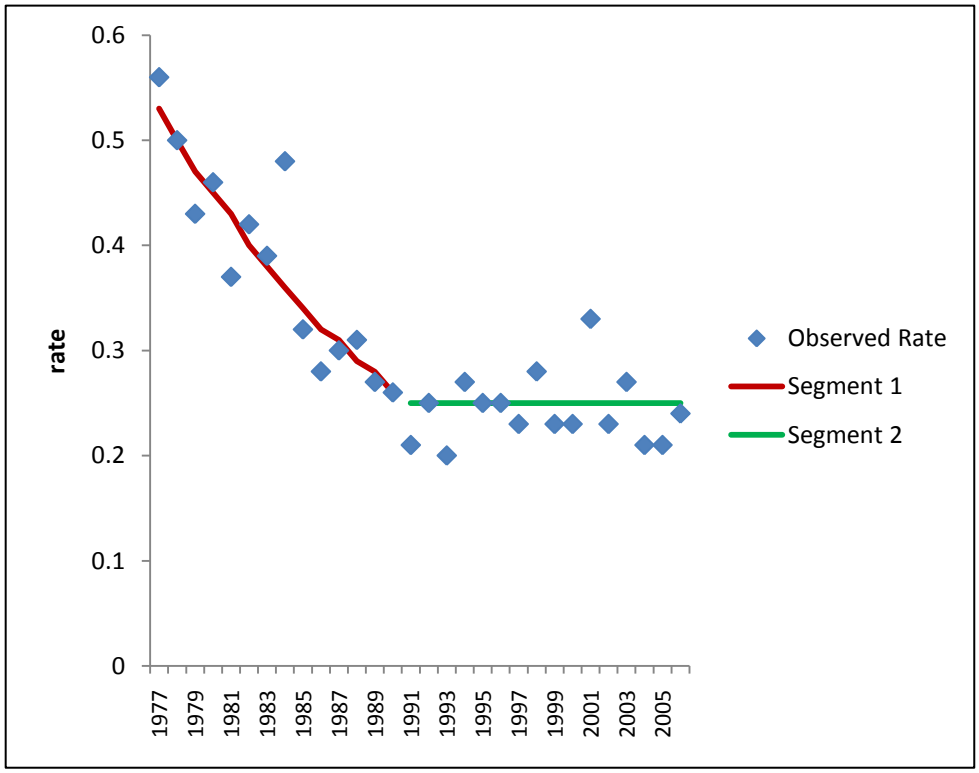
Figure 5-1 An observed trend for a rate (simulated data)



A joinpoint regression analysis on this data (Figure 5-2), found two distinct periods in the trend. The point of change has been located in 1991, with a 95% confidence interval of having occurred in 1987 or 1994. This point creates two segments of different rate of change. The first segment started in 1976 and ended in 1991 with an annual percent change of - 5.3% (95% CI -6.6% to -3.9%), statistically significantly different from a 0% rate of change.

The last segment of the trend shows a “flat” pattern, starting in 1991 and ending in 2006, where the annual rate of change was 0% (-1.7% to 1.7%). Models with 0, 2, 3 or 4 joinpoints were rejected using the Bayesian Information Criterion (BIC) approach for model selection. The key strength of this technique is to avoid the detection of biased patterns when the trend is described subjectively using observer defined time intervals. The observer might bias in several ways the choice of periods for estimating summaries of the rate of change of the trend, based on prior knowledge or because the trend shows curious patterns. Joinpoint avoids this by essentially removing the observer from the selection process, instead using a formal and objective exploration of the time-series data space.

Figure 5-2 Observed and joinpoint modelled rates (simulated)



In the next sections, I will use this approach to examine recent interesting phenomena observable in CHD mortality trends in a variety of different countries. Flattening of previously falling CHD mortality rates has recently been reported among young adults in the US, perhaps reflecting changes in specific risk factors. Since young adults in many other Western countries are also now showing complex risk factor trends, a similar flattening in mortality rates patterns is distinctly possible.

I will start by describing recent trends in CHD mortality in England & Wales, particularly amongst young adults, and then I will look for recent trend patterns in Australia and the Netherlands. Later I will examine recent trends in Poland and its determinants, and trends by socioeconomic status in Scotland and England.

5.3 CORONARY HEART DISEASE TRENDS IN ENGLAND AND WALES FROM 1984 TO 2004: CONCEALED LEVELLING OF MORTALITY RATES AMONG YOUNG ADULTS

5.3.1 Introduction

In the UK, mortality rates from coronary heart disease have continued to decline steadily since the late 1960s.[6] Improvements in population risk factors and in medical treatments for CHD patients have both contributed substantially to the declines seen between 1981 and 2000.[149] Nevertheless, coronary heart disease [CHD] remains the leading cause of death and exacts a heavy social and economic toll. Furthermore, concern has recently been expressed that in the USA the rate of decline in mortality from CHD has slowed during the 1990s compared to earlier decades.[210]

Does the UK risk follow US trends? The increases in the prevalence of obesity and diabetes in the UK since the 1980s are potential warning signs that the hard fought gains in cardiovascular mortality improvements might be arrested or even reversed.[211,212] Furthermore, the declines in total cholesterol concentrations during the 1990s have been modest, even though prescribing of statins has escalated.[213,214] Although tobacco use continues to decline, the adult prevalence of smoking still remains well above 20%; moreover, the large number of UK adults who are totally sedentary during leisure-time has probably increased since the 1990s.[213] As a result of these conflicting trends in the various risk factors, the earlier falls in CHD deaths may soon be blunted.[212]

Unfavourable trends in some cardiovascular risk factors have been particularly worrying among younger adults. Between 1993 and 2003, some of the largest relative increases in obesity and diabetes have occurred among adults aged less than 45 years. [213] Furthermore, mean concentrations of cholesterol dropped little or even increased among some of the younger age groups.[213] Moreover, the previous decline in smoking rates may be levelling off among young adults, the smallest reduction have been seen in men aged 25-34.[6] Thus, it is reasonable to hypothesize those adverse trends in CHD mortality rates may be detected first among young adults.

Although previous reports have emphasized the continuing declines in the age-adjusted CHD mortality rate among UK adults[6], trends in age-specific rates have received little attention. The objective of our study was therefore to examine trends in the age-specific rates for coronary heart disease among UK adults from 1984-2004, particularly among younger adults.

5.3.2 Methods

Vital statistics data were obtained for the England and Wales. [6,211] We limited our analyses to people aged 35 years and older. The underlying cause of death from coronary heart disease was determined using the International Classification of Diseases (ICD)-9 codes 410-414 for 1984-1998 and ICD-10 codes I20-I25 for 1999-2004. Population counts from the England and Wales census were used to calculate rates. We used census counts for the years 1981, 1991, and 2001 and inter-censal estimates for the other years. Age-adjustment was performed using the direct standardization method to the estimated England and Wales population of the year 2001.

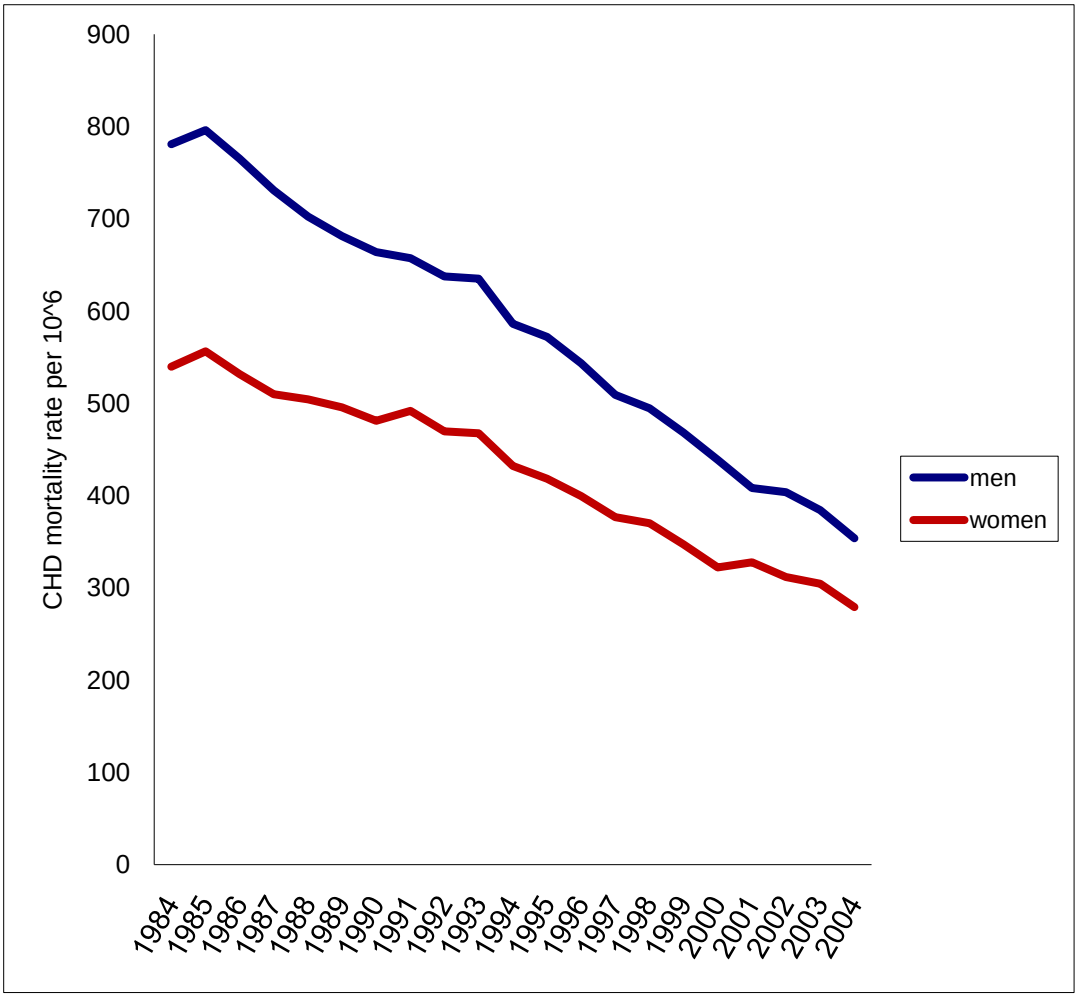
Plots of mortality rates were smoothed using 5-year moving averages. A Joinpoint regression was fitted to provide estimated annual percentage change and to detect points in time where significant changes in the trends occur (JOINPOINT software version 3.0), and we used a Bayesian Information Criterion (BIC) approach to select the most parsimonious model that fits best the data.[209,215] A maximum number of 3 joinpoints was allowed for estimations. For each annual percentage change estimate, we also calculated the corresponding 95% confidence interval (95% CI).

5.3.3 Results

The overall age-adjusted mortality rate for coronary heart disease declined from 1984 to 2004, by 54.7% in men and 48.3% in women (Figure 5-3). The average annual rate of decline for men was 2.7% during the 1980s increasing to 3.7% during the 1990s (1.7% in women increasing to 3.5%). From 2000 through 2004, the average annual rate of decline was even greater, 5.4% for men (and 4.2 % for women).

The overall age-adjusted rates concealed striking differences in the age-specific rates, as shown in Figure 5-4 and Table 5-1. Comparing the first and last period identified in the joinpoint regression analysis, the rate of decline has slowed for men aged 35-44 and 45-54 (reduction in the annual percent change of 35% and 47% respectively). Furthermore, for men aged 35-44, the annual percent change for the period 2000-2004 was not significantly different from 0, although is based on a period of 4 years . For older men (aged over 55), the rate of decline continued to increase throughout the period.

Figure 5-3 Trends in age-adjusted mortality rates from coronary heart disease for England and Wales adults aged 35+ years, 1984-2004



Among women aged 45-54, the annual percent change was reduced by about 39% in the period 1998-2004 (Table 5-1). Rates in the age group 35-44 apparently continued to decline however the numbers of events were very low. (Figure 5-5)

Data on model fit and selection is presented in Appendix 1A1. Both the BIC and the permutation test approach identified similar periods and estimated annual percent changes.

Figure 5-4 Trends in age-specific coronary heart disease mortality rates and 5 year moving averages for men aged 35+ years, England and Wales, 1984-2004

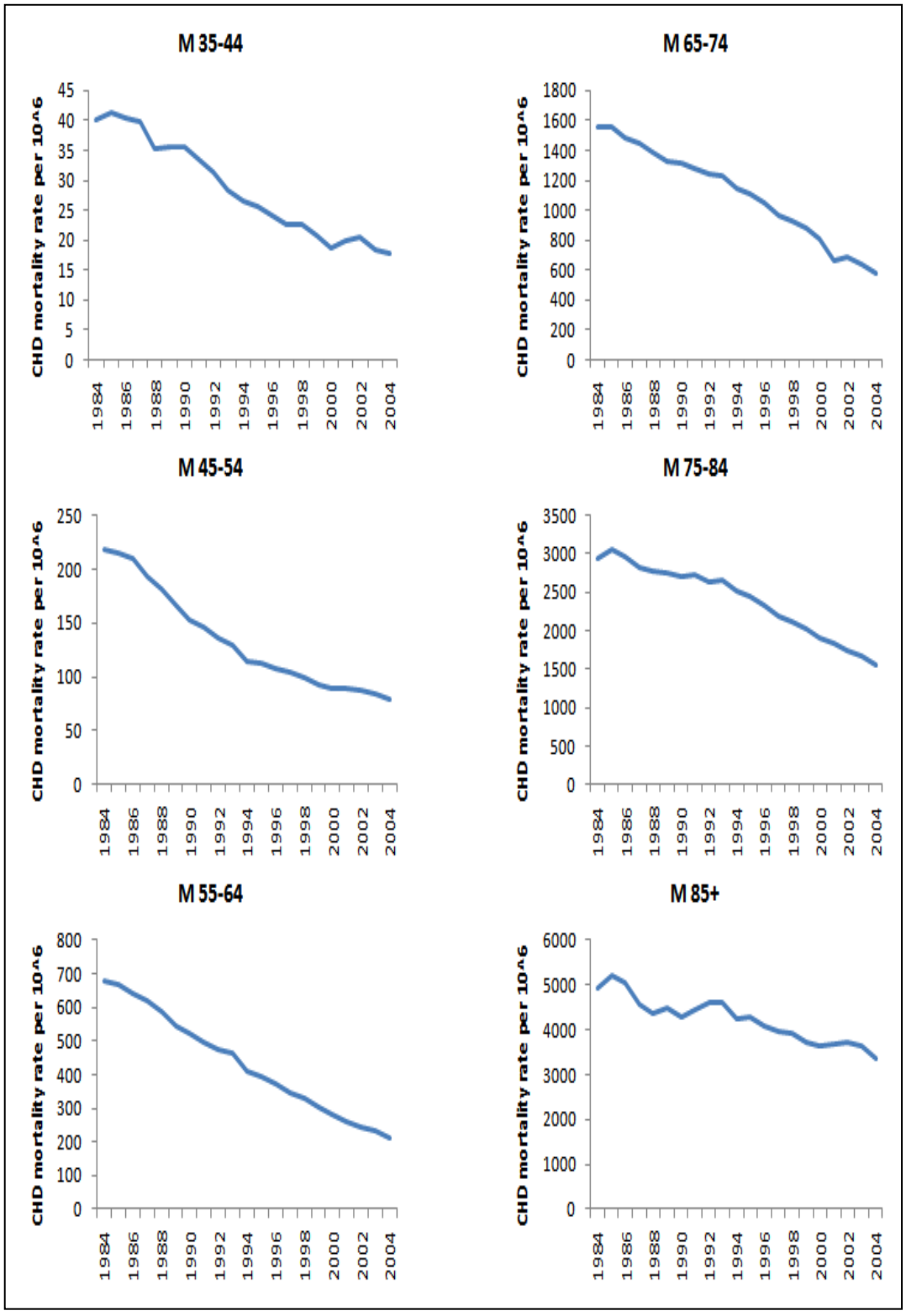


Figure 5-5 Trends in age-specific coronary heart disease mortality rates and 5 year moving averages for women aged 35+ years in England and Wales, 1984-2004

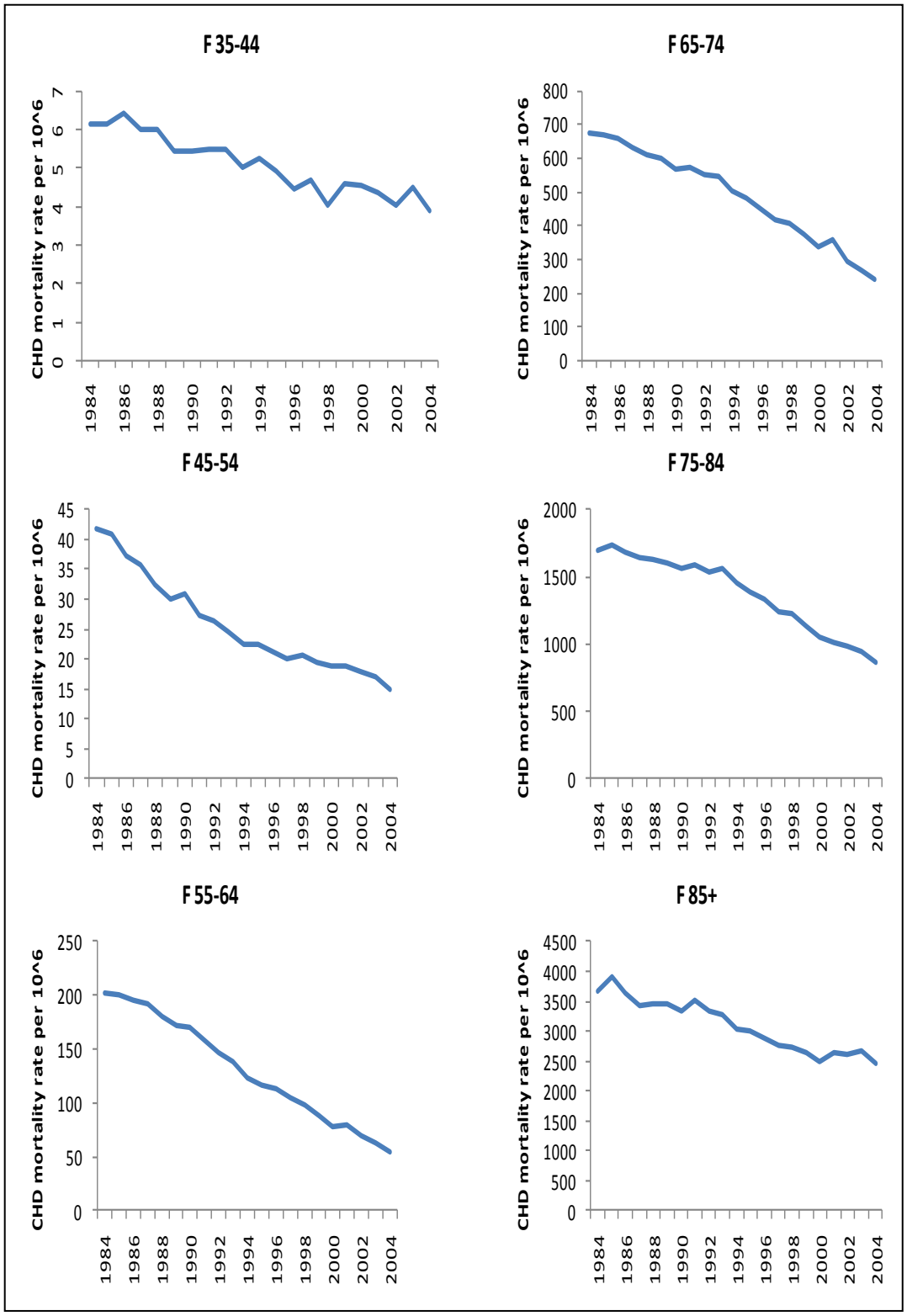


Table 5-1 Joinpoint analysis: Trends in age-specific coronary heart disease mortality rates England and Wales 1984-2004 [adults aged 35+ years]

	Men			Women		
	Period	EAPC	95%CI	Period	EAPC	95%CI
35-44	84-91	*-3.7**	*(-4.8,-2.6)*	84-04	*-3.2**	*(-3.6,-2.9)*
	91-00	*-6.9**	*(-7.91,5.8)*			
	00-04	*-2.4*	*(5.9,1.4)*			
45-54	84-87	*-3.4**	*(-5.6,-1.1)*	84-90	*-6.6**	*(-7.8,-5.3)*
	87-94	*-9.4**	*(-10.2,-8.5)*	90-95	*-8.9**	*(-11.6,-6.2)*
	94-99	*-5.8**	*(-7.8,-3.8)*	95-04	*-3.5**	*(-4.5,-2.5)*
	99-04	*-1.8**	*(-3.4,-0.2)*			
55-64	84-87	*-1.5**	*(-2.9,0.01)*	84-90	*-1.6**	*(-2.7,-0.5)*
	87-93	*-4.8**	*(-5.5,-4.5)*	90-98	*-6.6**	*(-7.6,-5.6)*
	93-98	*-6.4**	*(-7.8,-5.3)*	98-04	*-11.3*	*(-12.9,-9.6)*
	98-04	*-9.5**	*(-10.2,-8.8)*			
65-74	84-93	*-3.8**	*(-4.1,-3.5)*	84-92	*-2.8**	*(-3.3,-2.4)*
	93-99	*-4.8**	*(-5.7,-3.9)*	92-99	*-4.5**	*(-5.2,-3.7)*
	99-04	*-8.3**	*(-9.4,-7.2)*	99-04	*-8.3**	*(-9.5,-7.1)*
75+	84-89	*-4.6**	*(-5.8,-3.3)*	84-88	*-3.5**	*(-5.5,-1.4)*
	89-94	*-1.3*	*(-3.2,0.5)*	88-93	*0.9*	*(-3.1,1.2)*
	94-04	*-6.1**	*(-6.6,-5.6)*	93-00	*-4.9**	*(-6.1,-3.7)*
				00-04	*-2.7**	*(-5.2,-0.1)*

EAPC: Annual percent change
* Significantly different from 0

5.3.4 Interpretation

Recent trends for coronary heart disease mortality in younger UK adults are disquieting. The previous falls in age-specific mortality rates appear to be flattening in men and women aged less than 55 years. Thus far, rates in older adults continue to decline. These patterns are confirmed when formally examining the absolute annual changes in rates.

As I discussed in chapter 4, changes in CHD mortality rates generally reflect changes in incidence rate and, to a lesser extent, case-fatality rate. [20] Unfortunately, unbiased data about CHD incidence in the UK are limited, especially in younger groups. Studies using hospitalization rates represent a proxy that can be difficult to interpret. [216] However, population-based data from

Scotland and from the two UK MONICA centres reported substantial decreases in CHD incidence from the mid 1980s to the mid 1990s[20,217,218] which continued beyond 2000.[219] Case fatality following myocardial infarction has also improved since the mid 1980s. [20,220]

The flattening English coronary mortality rate trends during the 1990s among those aged under 55 years require explanation. These trends have occurred in spite of the increasing use of evidence-based therapies such as angioplasty, thrombolysis and angiotensin-converting enzyme inhibitors.[149] This suggests that unfavourable recent trends in risk factors in young adults may explain these changes, specifically increases in obesity and diabetes compounded by stable cholesterol levels and a smoking prevalence stubbornly persisting above 25%.[213] Material deprivation could be also an important factor in younger adults. In this age group, deprivation is strongly associated with CHD mortality and could be understood as an upstream risk factor for coronary heart disease acting through the established risk factors as mediators (see chapter 3).[221,222] This is a potential target population for intervention, although it could be more effective to influence risk factor prevalence through population level interventions.[223]

The flattening of the mortality trend in young adults I found in England & Wales is a recent phenomenon, and is consistent over 4 years. More evidence is needed, particularly to assess if this is a transient or an ongoing phenomenon. As we know that the phenomenon seems to be happening in the US, looking at trends in other countries could help to further understand it. The flattening trends in CHD mortality rates among younger adults, if continue, suggest that the cardiovascular disease epidemic is not being fully controlled. This is a crucial aspect that requires further attention.

In the next section, I will discuss recent Australian trend data, where evidence of flattening was first suggested in the 1990s in the youngest adult cohorts. This provides a unique opportunity to explore if the flattening is a transient phenomenon or a more sustained population process.

5.4 THE DECLINE IN CORONARY HEART DISEASE MORTALITY IS ALSO SLOWING IN YOUNG ADULTS IN AUSTRALIA (1976-2006)

5.4.1 Introduction

Australia has been one of the countries that experienced the decline in coronary heart disease mortality in the last four decades. CHD mortality has been continuously decreasing[116], as in most Western countries[194], with approximately 2/3 of the decline attributable to changes in risk factors and 1/3 to evidence based treatments.[20,144,148,224,225] In Australia and New Zealand, a larger proportion of the decline has been attributed to changes in risk factors, about 80%.[226,227]

Nevertheless, because of population ageing, coronary heart disease will continue to exert a heavy burden for both developed and developing countries. [228,229]

A slowing of the decline in coronary heart disease mortality is apparently occurring recently in young adults in the US[192] and in the UK (section 5.3). These changes probably reflect attenuation of declines, arrest or reversal of trends in major risk factors, since dramatic deterioration of medical care in this age group appears unlikely in developed countries.[192,230,231]

However, the changes in the USA, England & Wales showed these changes in the rate of decline only recently and for a period of 2 to 4 years. This raises the question about whether this phenomenon is sustained or transient.

In Australia, like in most Western countries, age-adjusted coronary heart disease mortality rates have also been declining over the last three decades. However, a report from Wilson et al suggested that the rate of decline for the most recent birth cohorts (aged 25-40 years in 1992) slowed or even ceased around the 1990s.[189]

The aim of the following section is therefore to examine more recent age and gender specific trends in Australian CHD mortality between 1976 and 2006, to look for evidence of continuation of the flattening reported in the 90s.

5.4.2 Methods

Vital statistics data including population numbers were obtained from the General Record of Incidence of Mortality (Australian Institute of Health and Welfare) for the period 1976 to 2006.[232]

The underlying cause of death from coronary heart disease was determined using the International Classification of Diseases (ICD) 8 and 9 codes 410-414 for 1976-1996 and ICD-10 codes I20-I25 for 1996-2006. Age-adjustment was performed using the direct method to the estimated Australian population of the year 2001.

We fitted a Joinpoint regression to provide estimated annual percentage change and to detect points in time at which significant changes in the trends occurred (Joinpoint Regression Program, version 3.4).[215] We used a BIC approach to select the most parsimonious model that best fitted the data allowing a maximum of three joinpoints for estimations. 95% confidence intervals were calculated for each estimate of annual percentage change.

5.4.3 Results

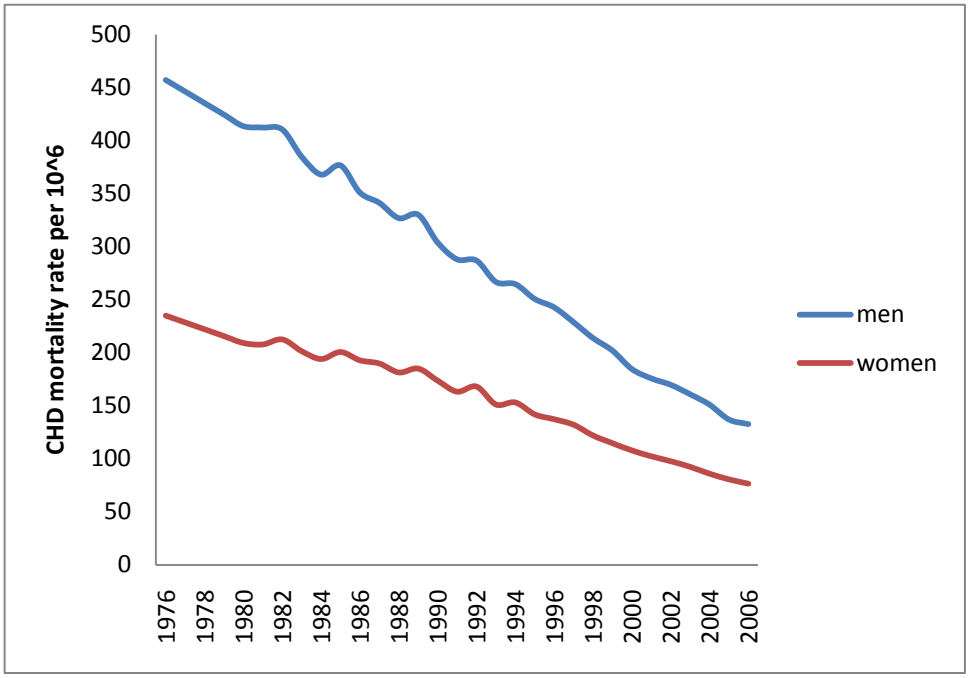
From 1976 to 2006, the overall age-adjusted mortality rate for coronary heart disease declined by 73% in men and 70% in women (Figure 5-6). The average annual rate of decline over the entire period was 4.3% for men and 3.9% for women. The last ten years showed a slightly higher average annual rate of decline 5.8% for men and women.

The age-adjusted rates concealed striking differences in the age-specific rates (Figure 5-7, Figure 5-8 and Table 5-2). The decline in mortality continued for men and women above 55 years. However, for men aged 25-34 years, the annual percentage change for the period 1991-2006 was not significantly different from 0 (95% CI:-1.6 to 1.6)(Table 5-2).

For men aged 35-44 the decline in mortality rates started in 1992 and the annual percent change was 61% less, comparing 1992-2006 with 1976-92. In men aged 45-54 years, the annual percent change was 44% less in 1994-2006 compared with 1976-94.

A similar flattening was also seen in young women. Among women aged 25-34 years, the rate mortality rate decline lessened from 1980 onwards, and the annual percent change was 97% slower in the period 1980-06 compared with the period 1976-80. Furthermore, for both periods the rate of decline was not significantly different from zero. For women aged 35-44 years, the annual percentage change in 1988-2006 decreased by 82% compared to 1976-1988. For women aged 45-54 years, the decrease in the average annual rate of change in the period 1991-2006 was 59% lower than in the period 1986-1991 (Table 5-2).

Figure 5-6 Trends in age-adjusted mortality rate from coronary heart disease for Australia, adults aged 25+ years, 1976-2006



5.4.4 Interpretation

The overall decline in age-adjusted CHD mortality rates in Australia since 1980 conceals an important change in younger adults. This recent slowing in the rate of mortality decline is occurring in both men and women aged below 45 years. This mortality flattening first occurred in the 1980s in the youngest age groups, and started later around 1991-1994 for those aged 45 to 54 years.

The attenuation in CHD mortality decline probably started in the early 1990s among male cohorts born between 1955 and 1964, as reported by Wilson et al[189]. The flattening in younger women was not initially apparent in this analysis. This probably simply reflects the different time periods analyzed by Wilson and in the way Joinpoint uses an unbiased statistical approach to best select the period of similar rate of change.

Figure 5-7 Observed and estimated trends in CHD mortality by age, Australian men 1976-2006

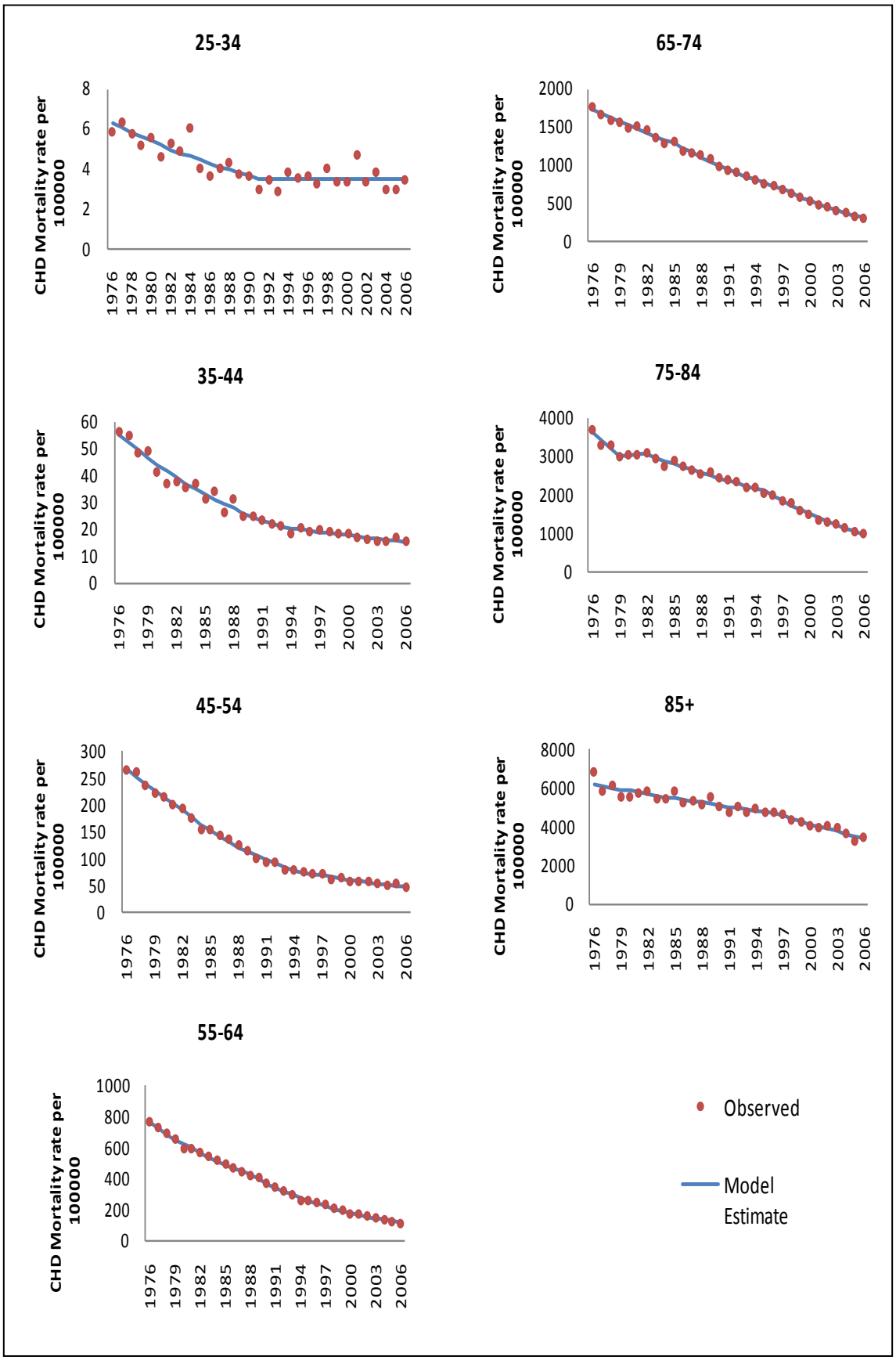


Figure 5-8 Observed and estimated trends in CHD mortality by age, Australian women 1976-2006

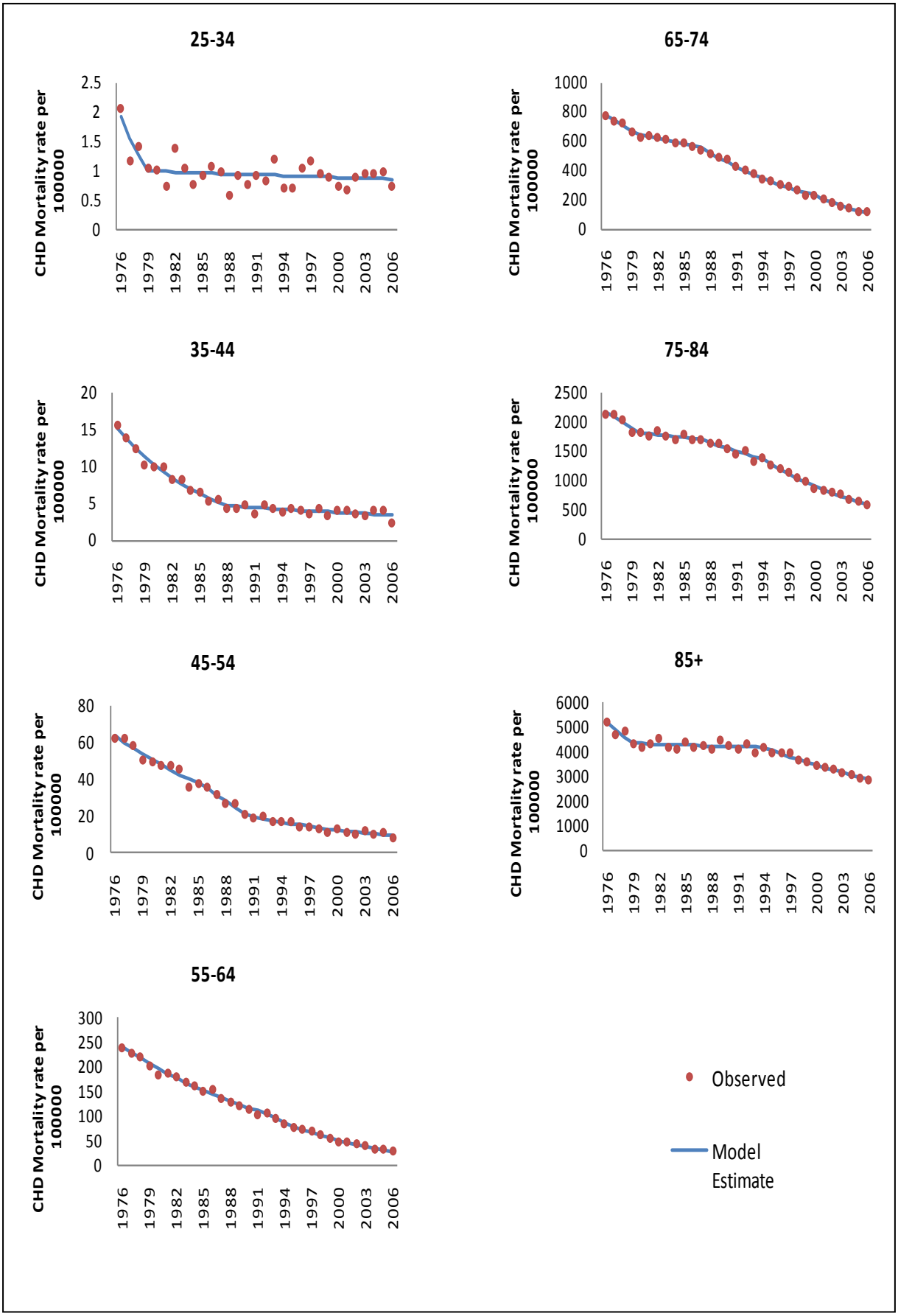


Table 5-2 Joinpoint analysis: Trends in age-specific coronary heart disease mortality rates in Australia 1979-2006 [men and women, aged 25+ years]

Men						Women					
Age	Period		EAPC	Lower CI	Upper CI	Age	Period		EAPC	Lower CI	Upper CI
25-34	1976	1991	-3.8*	-5.2	-2.3	25-34	1976	1980	-19.6	-36.4	1.7
	1991	2006	0	-1.6	1.6		1979	2006	-0.5	-1.5	0.5
35-44	1976	1992	-5.6*	-6.2	-5	35-44	1976	1988	-9.4*	-10.7	-8
	1992	2006	-2.2*	-3.2	-1.2		1988	2006	-1.7*	-2.7	-0.8
45-54	1976	1982	-5.6*	-6.6	-4.5	45-54	1976	1986	-5.7*	-6.8	-4.5
	1982	1994	-7.2*	-7.7	-6.6		1986	1991	-11.5*	-17	-5.6
	1994	2006	-4.0*	-4.5	-3.4		1991	2006	-4.7*	-5.7	-3.8
55-64	1976	1988	-4.7*	-5	-4.4	55-64	1976	1992	-5.1*	-5.4	-4.8
	1988	2006	-7.0*	-7.2	-6.8		1992	2006	-8.9*	-9.5	-8.3
65-74	1976	1985	-3.2*	-3.7	-2.7	65-74	1976	1980	-4.5*	-5.8	-3.2
	1985	1997	-5.0*	-5.4	-4.6		1980	1987	-2.1*	-2.8	-1.3
	1997	2006	-8.5*	-9.21	-7.9		1987	2000	-6.5*	-6.8	-6.2
							2000	2006	-11.2*	-12.4	-10.1
75-84	1976	1979	-5.8*	-9.3	-2.3	75-84	1976	1980	-4.4*	-6.8	-1.8
	1979	1982	0.2	-7	8		1980	1987	-1	-2.3	0.4
	1982	1995	-2.8	-3.1	-2.4		1987	1994	-3.0*	-4.3	-1.8
	1995	2006	-6.6	-7.1	-6.2		1994	2006	-6.6*	-7.1	-6.2
85+	1976	1996	-1.3*	-1.7	-1	85+	1976	1979	-5.7*	-10.3	-0.9
	1996	2006	-3.2	-4	-2.4		1979	1994	-0.3	-0.7	0.2
							1994	2006	-3.0*	-3.4	-2.6

CI: confidence interval. EAPC: Estimated annual percentage change. *significantly different from 0

These results are also consistent with findings described in other populations. In the US, Ford and Capewell[192] described a similar phenomenon in young men aged under 45 years, commencing in the 1990s, an in England & Wales trends as I described in section 5.3.

The reasons for the attenuation of the CHD mortality decline in Australia, the US and England & Wales remain unclear. A marked deterioration of clinical care in these high-income countries seems implausible. Indeed, in the US and the UK, the uptake of evidence-based treatment has been steadily increasing in recent decades, although there is room for further improvement.[144,225]

Probably the most plausible explanation must be adverse changes in trends in major CHD risk factors, reflecting lifestyle changes in young and middle aged adults. As I discussed in section 4.4, a growing body of evidence suggests that 45%-70% of the recent decline in CHD mortality could be attributed to a decrease in risk factors.[144,148,186,200,233] Furthermore it has been estimated in Australia and New Zealand, using a different methodology, that the decline in risk factors could explain 74% of the decline in CHD mortality in men`, and 84% in women.[226,227]

Might age specific differences in risk factor changes therefore perhaps explain these recent differences in the rate of decline by age? In Australia, risk factor trends over the last decades have shown a complex picture. Blood pressure and serum cholesterol have all decreased across the entire population[226] in men and women from 1990 to 2001. The proportion of energy consumed as fat has also been decreased significantly over the period.[234,235]

Smoking reached a nadir of 16% during this period, but smoking in young adults continues to be a significant problem.[236] However, diabetes mellitus increased significantly in Australia, between 1991 and 2003, with the greatest increases (139%) seen in obese adults aged under 60 years.[236]

Is this attenuation of the decline in CHD mortality simply an artefact of low rates? It could be postulated that as rates progressively decline, a "background" incidence will be reached making further mortality reductions impossible. However, our current understanding of CHD causation strongly suggests that this is not the case because far lower coronary heart disease mortality rates have been observed in the subset of individuals with low levels of risk factors in several large cohorts.[136] I will discuss later (chapter 7) that the existence of socioeconomic differentials again suggest that this is a real phenomenon.[237] Moreover, the log-linear relationship demonstrated between major CHD risk factors and CHD mortality suggests that any baseline threshold is very low indeed.[238,239]

This study has limitations. Since most of the trend changes were recent, the confidence intervals for their average annual percent changes were correspondingly wide. It is therefore important not to exaggerate the significance of these changes. The wide confidence interval encompassing zero means that a flat line is possible, but not 100% certain.

There is also potential for disproportionate miscoding of mortality in the young. However, Lozano et al.[185] studied the proportion of ill-defined codes that could result in misclassification of ischemic heart disease deaths in several countries and calculated correction factors by age and gender. Globally, for those under 50 years of age, the correction needed is less than 5%. Furthermore, this study found that Australian observed rates were equal to the corrected ones suggesting that the quality of coding, particularly among the young, is high.[185]

One of the strengths of the present study is the use of Joinpoint as an unbiased approach to detect points in time where a significant change in the annual percent change in mortality rates happened. Furthermore, our approach confirmed the earlier Wilson study that used a very different methodology.[189]

Most evidence therefore supports the idea that coronary heart disease mortality rates in young adults can decline substantially further. These changing trends are clearly dynamic and need continuous monitoring. Furthermore, as this cohort ages, they will reach a proportionately higher cardiovascular risk. We therefore need to explore and better quantify the exact relationship with mortality and risk factor trends in population subgroups defined by age, gender and socioeconomic status in order to determine optimal preventative strategies. These emerging data are therefore likely to further strengthen growing calls for more effective policies for cardiovascular disease prevention. Should we target specific age groups? Although this approach may appear superficially attractive, population-wide policies (such as smoke-free legislation, transfat eradication and reductions in the salt and saturated fat content of processed food), could be much more effective in reducing the risk across all age and gender groups, while reducing socio-economic inequalities in disease burden and actually saving costs.[240]

The flattening of trends in young adults suggests that hard won gains can be rapidly lost. However, rates are not set in stone, they are dynamic and these changes could be as well reversed. In the next section, I will present evidence of flattening and a later recovery of the decrease in mortality in the Netherlands. Its particular interest resides in the often overlooked speed at which the coronary heart disease epidemic can change course.

5.5 AGE-SPECIFIC PATTERNS IN THE NETHERLANDS

5.5.1 Introduction

The Dutch population experienced a decline in the age adjusted coronary heart disease mortality rates since the 1970s. As in other Western countries, the increased use of evidence base treatments and beneficial trends on physical activity[241], cholesterol and dietary intake of fats[242], were offset by adverse trends in diabetes and obesity.[243] Little data on age specific risk factor trends is available, but as in many countries, smoking is still prevalent in young adults with modest declines compared to other age groups.[244]

The aim of the analyses presented here was to explore recent coronary heart disease mortality trends in the Netherlands to verify if the flattening observed in some Western countries has also occurred in this country.

5.5.2 Methods

Data for all CHD deaths (1972-2007) were provided by Statistics Netherlands and grouped by year, sex and age. The eighth version of the ICD was used for the years 1972 to 1978 (ICD codes 4100-4149), the ninth version for the years 1979 to 1995 (ICD codes 4100-4149) and the tenth version (ICD codes I20-I25) thereafter. Age adjusted rates were calculated using the European standard population.[245] All analyses were performed in accordance with privacy legislation in the Netherlands.[246]

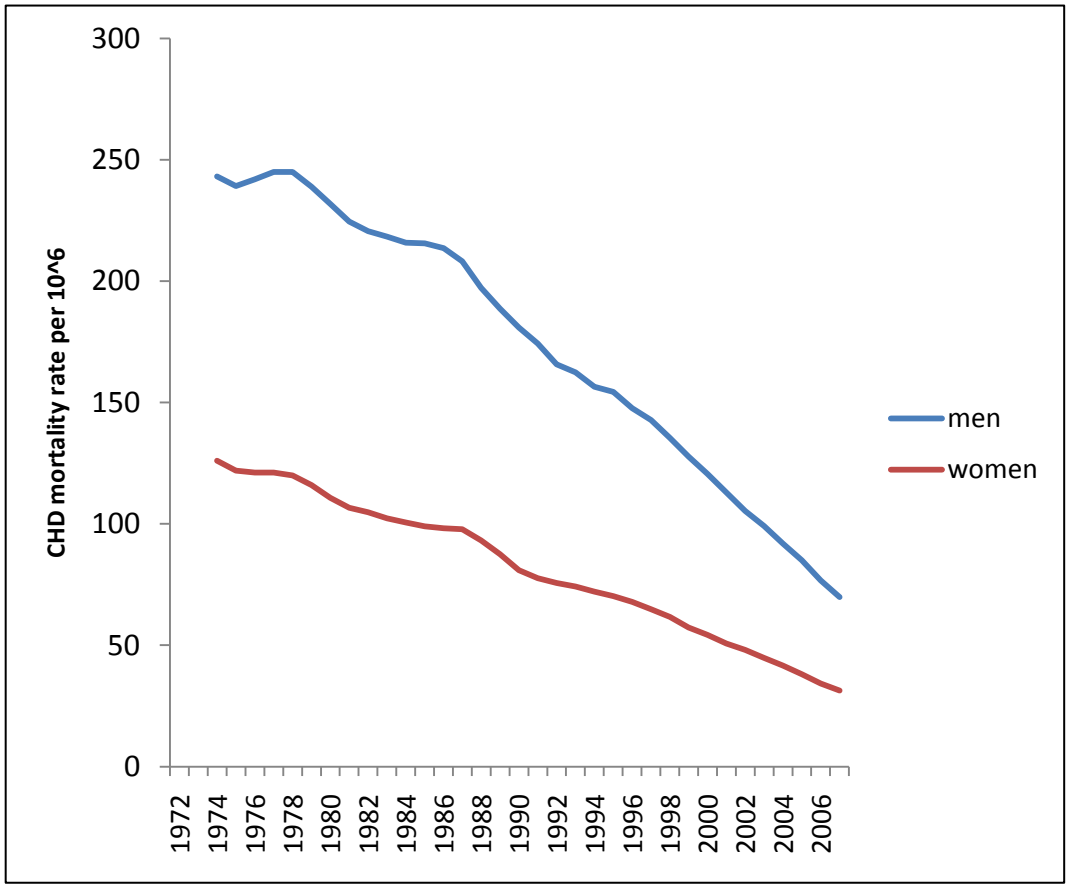
A joinpoint regression was fitted to each age-sex-group to detect points in time at which significant changes in the trends occur.[215] For every time period, we calculated the annual percent change, p-value, observed number of deaths, CHD mortality rates and the change in CHD mortality rate.

5.5.3 Results

Between 1972 and 2007, the age-adjusted coronary heart disease mortality rates decreased overall by 75.6% in men and 75.7% in women (Figure 5-9). The average rate of decline in men was -1.65 (95%CI -2.0% to -1.2%) from 1972 to 1985, -4.0% (95% CI -4.3% to -3.6%) from 1985 to 1999, and for the period 1999 to 2007 -7.3% (95% CI -8.0% to -6.5%). For women, the average rate of decline was -1.5% (95% CI -3.1% to 0.1%) from 1972 to 1977, -3.0% (95% CI -3.2% to -2.8%) from

1977 to 1996, -5.3% (95% CI -6.8% to -3.8%) for the period 1996 to 2002 and -8.1% (95% CI -9.5% to -6.6%) for 2002-2007.

Figure 5-9 Age standardised coronary heart disease mortality rates in the Netherlands by gender, 1972-2007



CHD mortality rates varied between the different age groups (Figure 5-10 and Table 5-3). In men aged over 55 and women aged 55 to 84, the decline started in the mid 80s, with constant increases in the rate of decline. However, in both men and women under 55, the trend followed a different pattern. After a decline started in both men and women around 1980, the rate of change flattened significantly after 1993 in men (EAPC for 1993-1999: -2.5%, -5.0% to 0.0%) and after 1989 in women (EAPC for 1989-2000: -0.1%, -1.5% to 1.3%)(Table 5-3).

At the beginning of the new century, both men and women under 55 years resumed the decline, with estimated annual percent changes of -7.6% (-8.7 to -6.4) for men and -7.3% (-9.5 to -5.0) for women (Table 5-3)

Figure 5-10 5-years smoothed CHD mortality rate per 100,000 by age group, men and women, 1972-2007

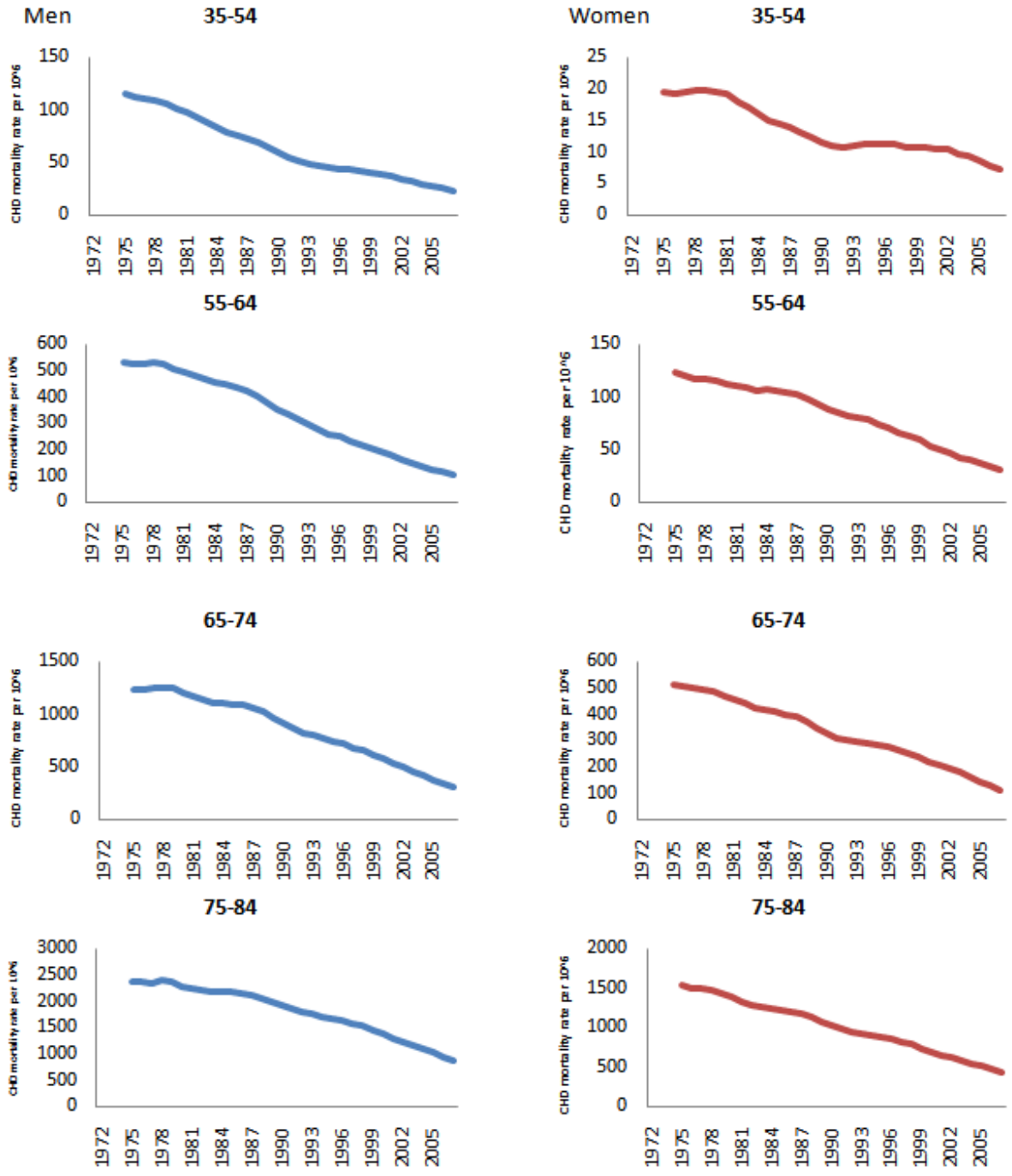


Table 5-3 Coronary heart disease mortality trends by age in the Netherlands, 1972-2007 for men and women aged over 35 years

Men						Women					
Age	Periods	Number of deaths (min-max)	Rates (min-max)	EAPC	95%CI for EAPC	Age	Periods	Number of deaths (min-max)	Rates (min-max)	EAPC	95%CI for EAPC
35-54	1972 – 1980	1556–1898	95.2-128	-2.8*	-4.0 to -1.5	35-54	1972 – 1979	273-319	18.2-21.1	0.1	-2.3 to 2.6
	1980 - 1993	981-1556	45.2-95.2	-5.7*	-6.4 to -5.1		1979 – 1989	207-302	10.8-19.4	-5.7*	-7.2 to -4.1
	1993 - 1999	918-1002	38.1-45.2	-2.5	-5.0 to 0.0		1989 – 2000	200-280	9.8-12.0	-0.1	-1.5 to 1.3
	1999 - 2007	520-939	20.7-38.1	-7.6*	-8.7 to -6.4		2000 - 2007	156-244	6.3-10.2	-7.3*	-9.5 to -5.0
55-64	1972 -1985	2814-3220	431-564	-1.8*	-2.4 to -1.3	55-64	1972 -1985	714-932	101-131	-1.6*	-2.3 to -0.9
	1985 -1998	1540-2949	206-483	-5.9*	-6.5 to -5.3		1985 -1996	476-771	64.9-106	-3.9*	-4.9 to -2.8
	1998 - 2007	958-1541	93.5-206	-8.1*	-8.9 to -7.2		1996 - 2007	254-509	25.1-68.8	-8.0*	-8.9 to -7.2
65-74	1972 – 1985	4726-5265	1086-1285	-1.3*	-1.8 to -0.8	65-74	1972 – 1987	2095-2674	311-539	-2.2*	-2.7 to -1.7
	1985 - 1999	3028-4794	559-1094	-4.4*	-4.8 to -3.9		1987 – 2000	1324-2095	205-311	-4.0*	-4.5 to -3.5
	1999 - 2007	1501-3028	243-559	-9.6*	-10.5 to -8.7		2000 -2007	668-1324	99.7-205	-10.6*	-12.0 to -9.2
75-84	1972 – 1985	4177-4693	2113-2497	-1.1*	-1.5 to -0.7	75-84	1972 – 1985	3718-4421	1205-1635	-2.3*	-2.7 to -2.0
	1985 – 1996	3730-4693	1581-2294	-2.8*	-3.4 to -2.2		1985 – 1996	3497-4426	820-1207	-3.4*	-4.0 to -2.8
	1996 -2003	3157-3895	1079-1581	-5.2*	-6.5 to -3.9		1996 – 2003	2501-3497	529-820	-5.7*	-6.9 to -4.5
	2003 - 2007	2412-3157	745-1079	-8.8*	-11.0 to -6.4		2003 - 2007	1831-2501	373-529	-8.7*	-10.8 to -6.5
85+	1972 -1998	1371-1638	2665-4351	-1.7*	-1.9 to -1.4	85+	1972 – 1977	1653-1958	3073-3311	-0.9	-2.5 to 0.7
	1998 - 2007	1266-1481	1875-2669	-3.9*	-5.0 to -2.8		1977 – 1980	1916-2083	2494-3077	-5.3	-11.9 to 1.8
							1980 – 1998	1932-2961	1747-2562	-2.0*	-2.3 to -1.8
							1998 - 2007	2178-2879	1147-1747	-4.7*	-5.3 to -4.1

EAPC: estimated annual percent change

*APC significantly different from 0%

5.5.4 Interpretation

The attenuation of the decline in CHD mortality among young Dutch adults in the 1990s is clearly evident and continued over several years. However, unlike the flattening described in the US, England & Wales and Australia, it was subsequently followed by a more recent period of decline.

In contrast to the other countries that had shown evidence of the flattening of mortality rates over the 1990s, this is the first country where a further decline in CHD mortality rates was observed after a plateau in mortality, particularly amongst younger adults.

The flattening in the Netherlands occurred despite the increasingly wide use of evidence based treatments, including lipid-lowering drugs[247], and increased physical activity[241,248], decreased cholesterol levels, and decreased dietary intake of saturated fat[242] during this period. This suggests that adverse trends in unfavourable risk factors, especially obesity and diabetes, compounded by persistent smoking, may powerfully contribute to changes in CHD mortality rates.[242,243].

The recent period of resumed decline is more difficult to explain. Data on changes in risk factors in the Netherlands since 2000 are limited, but indicate that the prevalence of obesity may have stabilised.[249] Furthermore, smoking prevalence[250] further decreased after being relatively stable during the 1990s.[251] These changes may have contributed to the more recent downward trend in CHD mortality.

Crucially, the trends in the Netherlands along with other countries, suggest that a decline in CHD mortality rate trends can change very quickly.[186,252,253] The pattern of flattening followed by resumed decline suggests that changes in the mortality rate can happen over relatively short periods of time, and an adverse trend can be turned into a favourable one rather quickly.

There is growing evidence that such changes can occur very soon after alterations in risk factors. For example, in Poland steady increases in mortality due to coronary heart disease were succeeded by a rapid decline observed between 1991 and 1994. [252,253] This followed dramatic dietary changes in 1989 and 1990 with increases in the ratio of polyunsaturated fat to saturated fat, and in fruit consumption. Similar changes happened in neighbouring countries including the Czech Republic Hungary and East Germany.[253]

5.6 CONCLUSION

The slowing in CHD mortality falls described in the USA, England and Wales and the Netherlands appears to be real, and probably not an artefact. Because clinical care over the periods studied improved, adverse changes in cardiovascular risk factors clearly represent the most plausible explanation for these patterns.

In the next chapter, I will study the recent trends in Polish CHD mortality. Poland offers a potentially unique opportunity to gain insights into the drivers of one of the most dramatic reversals of an adverse CHD mortality trend, happening alongside a complex transition to a market economy from a heavily centralized and subsidized environment.

I will then use the IMPACT model to formally explore and quantify the contribution of risk factors and evidence based treatments to the observed decline in Poland.

6 CHD MORTALITY IN POLAND: RECENT TRENDS AND POSSIBLE DRIVERS

6.1 INTRODUCTION

In this chapter, I will study an interesting natural experiment: the rapid decline in CHD mortality rates experienced by Poland since the 1990s. Substantial changes in CHD mortality happened in Poland after the transition to a market economy from a centralised, programmed and heavily subsidized society. As the Polish society becomes increasingly "Westernized" and integrated into the European Community, the trends in CHD mortality might eventually change their course and become more similar to rates observed in Western European countries. Continued monitoring of recent trends and understanding their drivers is therefore essential, not least to detect the first signs of any reversal of the huge gains achieved in this country.

I will begin by studying recent trends in age adjusted and age specific trends with the aim of seeking evidence of a change in the pace of decline in age-adjusted and in age specific rates. Then, I will use the IMPACT model to explore and quantify the contribution of risk factor changes and treatment to the observed decline.

6.2 ARE CHD MORTALITY RATES IN POLAND CONTINUING TO DECLINE?

6.2.1 Introduction

Poland experienced an interesting pattern in coronary heart disease mortality in the 20th century. During the Socialist era, coronary heart disease mortality rates increased at a steady pace.

However, a marked and sudden decline in cardiovascular disease deaths started in the early 1990s, paralleling the huge socioeconomic changes following the disintegration of the former Soviet

Union and the collapse of the communist economies in central Europe. Was this a coincidence or a causal association?

This abrupt mortality fall has been attributed in an ecological study to contemporaneous decreases in the consumption of saturated fats (as a result of rapidly disappearing state subsidies) and the increase in fruit & vegetable availability, accompanied by the increase in imports of "exotic" fruits.[252]

Poland in the 1990s can be viewed as a vast natural experiment, with reductions of key coronary heart disease determinants at a massive scale resulting in an abrupt change in direction of the mortality secular trend.

I have previously discussed the recent phenomenon of the "flattening" of coronary heart disease mortality rates in several countries (England & Wales, Australia, United States of America, Netherlands), and the rapid resumption of the downward trend in one country (The Netherlands). Because Poland is becoming an increasingly Westernized country, my aim was to explore if the decline in mortality rates seen in the early 1990s has continued, or whether there is any evidence of a slowing in the mortality decline in specific age and gender groups, as elsewhere.

6.2.2 Methods:

CHD mortality rates for the Polish population were obtained from the Polish Central Statistical Office, for the period 1982-2006, and corrected by Jasisnki et al for the period 1991-2006. [254] This correction is needed because officially reported data showed a peculiar pattern. While cardiovascular disease rates declined since 1991, ischemic heart disease rates apparently increased. However, there was a substantial change in cause of death coding and certification in 1997 (adoption of ICD 10 and regional coding by qualified coders). This resulted in an apparent increase in the number of ischemic heart disease deaths after 1996, but which was attributable to the frequent use of "atherosclerosis" as cause of death before 1996, primarily at the expense of specific ischemic heart disease and cerebrovascular disease codes.

Jasinski et al therefore used a regression model to estimate the number of ischemic heart disease in the period 1991- 2006. Their model uses individual death records from the Central Statistical Office (CSO) and data from the WHO Mortality Database. It includes terms to reflect the coding error for two periods (before and after 1997) and terms for the time trend based on the cardiovascular disease rates trends. The level of underestimation of ischemic heart disease dates in

the uncorrected data, before 1996 is about 35%, compared to the figures obtained with the regression modelling, with errors more significant in those older than 75 years, where the error was between 50-72%, in men and women.

I analysed the corrected, age- adjusted and age specific coronary heart disease mortality trends (using the Polish Population in 1982 as the population standard). I have used Joinpoint regression[209] to indentify periods of time with similar annual percent change in the rate. Model selection was performed using the Bayesian Information Criterion approach. Rates were smoothed using 3 years averages.

6.2.3 Results:

Age adjusted mortality rates:

CHD mortality started to decline dramatically in 1991 (lower and upper estimate of change year: 1984-1992) in men and in 1992 (lower and upper estimates of change year: 1987-1994) in women. Since 1991, CHD mortality rates decline 34.4 % in men and 33.8% in women. Both in men and women the trend continued to decline, although in women at a slightly lower pace since 2002. (Table 6-1 and Figure 6-1)

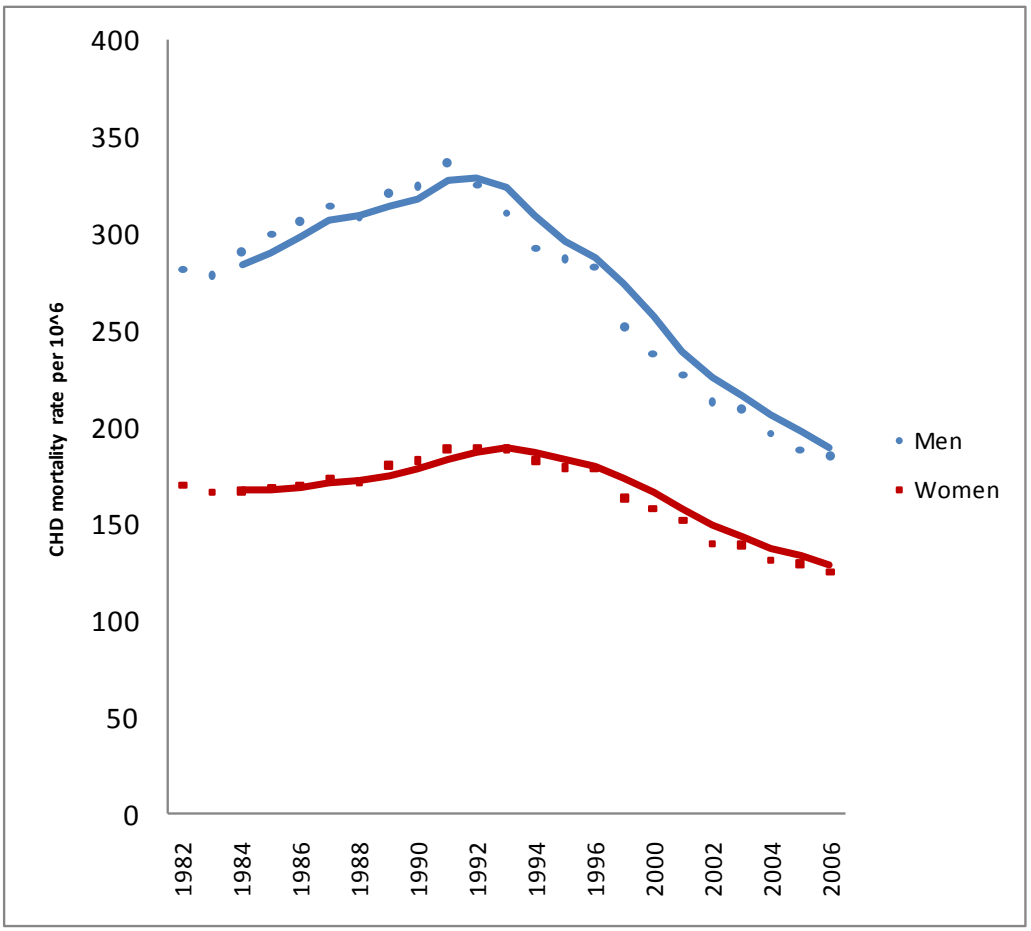
Table 6-1 **Joinpoint analysis: Poland, men and women age adjusted CHD mortality rates**

	Period Lower Endpoint	Period Upper Endpoint	EAPC	EAPC CI	
				Lower CI	Upper CI
Men	1982	1991	2.0*	1.6	2.4
	1991	1999	-3.6*	-4.6	-2.6
	1999	2006	-4.4*	-5	-3.9
Women	1982	1986	0.1	-1.2	1.4
	1986	1992	2.1*	1.2	3.1
	1992	1999	-2.0*	-3.3	-0.8
	1999	2002	-5.0*	-8.8	-1
	2002	2006	-3.2*	-4.4	-1.9

EAPC: estimated annual percent change

*APC significantly different from 0

Figure 6-1 **CHD Mortality rates in Poland, men and women aged 35+**



Age specific rates showed a different pattern, with all age groups showing declines starting in the 1990s (See Table 6-2 and Figure 6-2).

The coronary heart disease mortality rate for men under 54 years old rate changed abruptly in 1991 (1990-1992). The first period from 1982 to 1991 showed essentially an increasing trend, but since 1991 it showed a period of constant decline of 5.8% per year (95%CI 6.1-5.4).

Men over 75 showed a more complex pattern, although the rate of change was not statistically significantly different from 0, but declining from 1993 onwards. In women a similar pattern is noted, with marked declines since 1991 in those under 75, accelerating towards the year 2000.

Figure 6-2 Coronary heart disease mortality rates in Poland 1982-2006, by age and gender

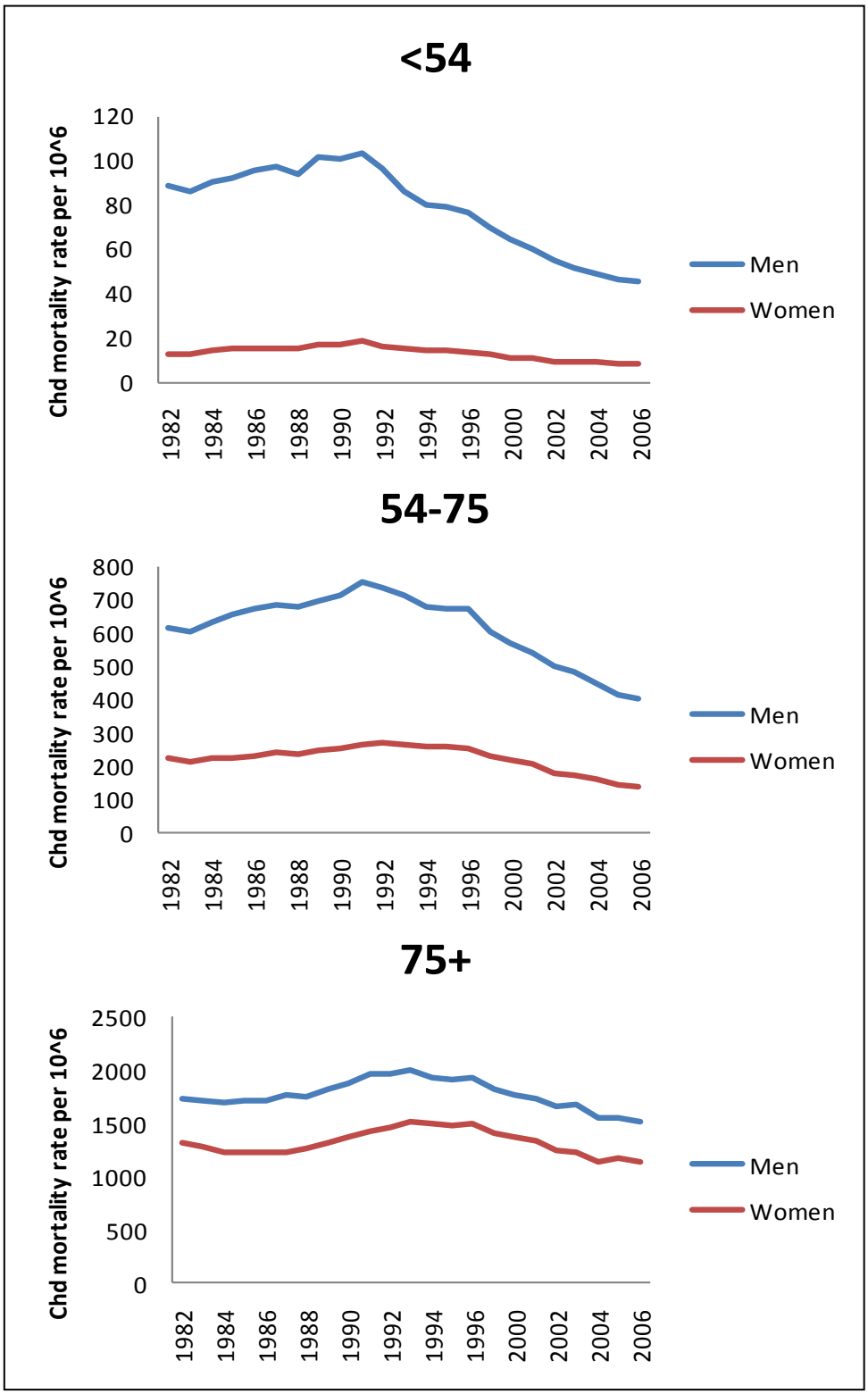


Table 6-2 CHD mortality trends by age in men and women, Poland 1982-2006 (joinpoint analysis)

Age	Period		EAPC	EAPC	
				Lower CI	Upper CI
			Men		
<54	1982	1991	1.1*	0.4	1.8
	1991	2006	-5.8*	-6.1	-5.4
54-75	1982	1991	0.4	0	0.8
	1991	2000	-2.8*	-3.4	-2.2
	2000	2006	-7.7*	-8.6	-6.8
75+	1982	1984	-5.4	-10.7	0.1
	1984	1989	-0.4	-2.2	1.4
	1989	1993	5.7*	2.9	8.6
	1993	1996	-1.8	-6.9	3.7
	1996	2006	-6.2*	-6.8	-5.6
			Women		
<54	1982	1991	2.9*	1.9	3.9
	1991	2006	-5.5*	-5.9	-5
54-75	1982	1992	0.9*	0.4	1.4
	1992	2000	-2.4*	-3.3	-1.5
	2000	2006	-9.0*	-10.1	-7.9
75+	1982	1987	-4.4*	-5.9	-2.9
	1987	1993	4.6*	3.1	6.2
	1993	1996	0.4	-5.8	7
	1996	2006	-6.8*	-7.5	-6.1

EAPC: estimated annual percent change

* APC significantly different from 0%

6.2.4 Interpretation:

Analysis of age-adjusted mortality trends confirmed the observation that the declining phase of the coronary heart disease epidemic in Poland started abruptly at the beginning of the 1990s, as described by Zatonski et al, and that this fall continues up to and including 2006, the most recent year studied. Men and women showed a period of marked decline in 1991-2006 in all age groups; but the speed of decline increased later on in adults older than 54. The oldest age group (75+)

appeared to start its decline a few years later. Furthermore, there was no evidence of a significant slowing down in any age group.

The lack of striking age patterns regarding the start of the decline suggests that this is a strong period effect, showing effects of similar magnitude across the age ranges.

Other countries in the region demonstrated similar changes in their mortality, and all experienced similar socioeconomic events in the same decade.[187]

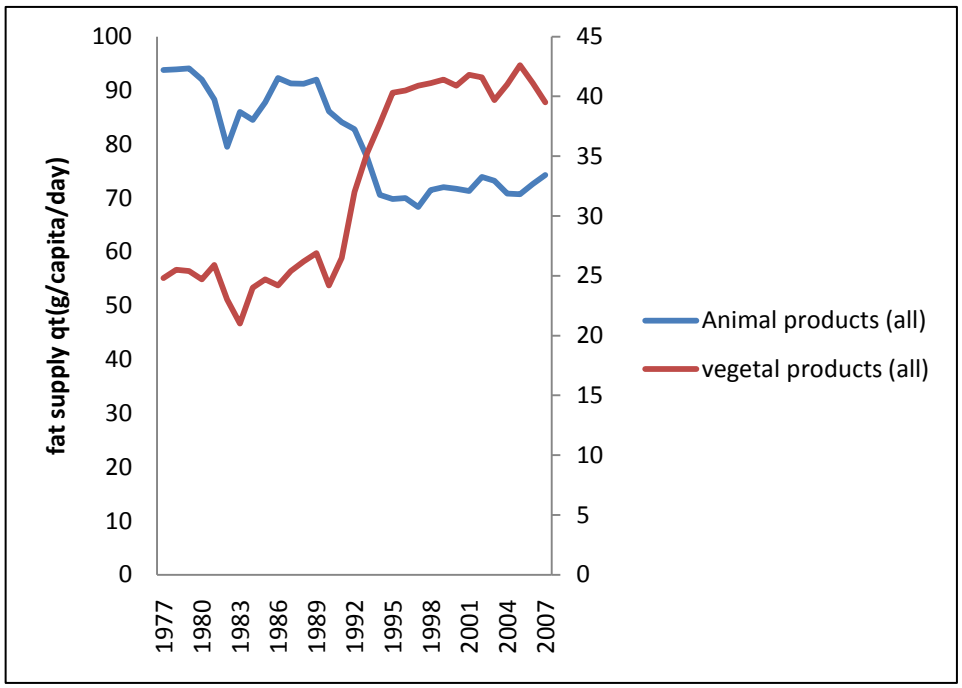
Although in the 1990s the access to evidence based therapeutic interventions for coronary heart disease was limited compared to the Western world[252], in recent years the uptake of those interventions have risen.[255-257] Risk factor trends over the period of decline however showed a complex picture. While there were significant declines in total cholesterol, physical activity and systolic blood pressure (only in women), diabetes obesity and systolic blood pressure (in men) showed alarming increases.[258-261] I will further assess the contribution of risk factors and treatments to the period of decline in the next section.

In Poland, food was no longer subsidised after 1990; this caused big changes in relative prices. Consequently, the structure of food consumed by Polish citizens changed substantially. For example, between 1989 and 2008 yearly butter consumption decreased from 7 kg to 3.8 kg per capita, and beef consumption fell by 75%. At the same time availability and consumption of fruits increased markedly.[252] Recent Food and Agriculture Organization food balance sheet data showed that the supply of fat from animal products (as a proxy for saturated fat supply) decline about 20% since 1991, while the supply of fat coming from vegetable products almost doubled. (Figure 6-3)

Interestingly, the change point in time for both the mortality rates and a proxy of the exposure of key determinants of coronary heart disease incidence are almost the same, 1991 (Figure 6-3). Since the effect of therapies is was small at that time (and increased thereafter), the changes in risk factors for the disease possibly triggered over a very short period of time(years), one of the most striking reductions in coronary heart disease mortality in the world.

The changes in Poland and its neighbouring countries were revolutionary, quite unlike those observed in any Western European countries at this time. The socio-economic changes in Poland 1991 and 2005 reflected substantial increases in GDP per capita. This increased four-fold in Poland (from 1 998 USD to 7 963 USD) but only two-fold in UK (from 18 387 USD to 36 084 USD, respectively).[262]

Figure 6-3 Fat supply quantities by origin (g/capita/day). Poland 1977-2007 (FAO, 2010)



On the other hand, shortly after the democratic transformation, citizen's purchasing power increased substantially, while inequalities increased modestly. [262,263] This might have resulted in an increased access to healthier foods. In Russia and Ukraine, by contrast, such inequalities increased sharply in the 1990s, and their mortality experience was crucially different.[262]

These disparities among countries experiencing very different socioeconomic environments translating in different mortality experiences suggests that mortality trends are associated to changes in the socioeconomic environment. The association between socioeconomic status and risk factor levels and differential access to health care is well know, suggesting that both the speed, direction and magnitude of trend changes might be also socially patterned. For example, there is evidence that differences in the time of onset of the decline phase of the CHD epidemic can be explained by socioeconomic characteristics in the US. [264] I will further elaborate this topic in chapter 7.

The decline phase of the CHD epidemic has been studied exhaustively in Western countries, well after the peak year of the epidemic. Poland offers the unique opportunity to study the decline phase but almost from its beginning. In the following section, I will use the IMPACT model to estimate the contribution of risk factors and evidence based treatments to the abrupt decline in CHD mortality experience by Poland since the 1990s.

6.3 USING THE IMPACT MODEL TO EXAMINE THE ABRUPT RECENT DECLINE IN CORONARY HEART DISEASE MORTALITY IN POLAND

6.3.1 Introduction

In the previous chapters, I have examined the dynamism of CHD mortality trends in several settings. Trends can fluctuate over time, sometimes quite rapidly in the matter of a few years. I also discussed some compelling arguments suggesting that changes in risk factors rather than evidence-based treatments might be the major drivers of these rapid changes.

However, our current understanding of coronary heart disease causation suggests that coronary heart disease development is a long process, probably taking the entire life course of individuals. Correspondingly, a change in risk factors will be followed after several decades by a change in mortality. Consequently, the rapid trend changes I described so far seem to not fit adequately within this framework.

Most of the research on the drivers of these trends in coronary heart disease rates has been conducted in Western countries, with longstanding declining trends. Generally, studies looked at trends well after the peak of the epidemic has been reached. For example, for the US studies this question was addressed over the period 1980-2000[144,200], while the peak of incidence was observed in mid 1960s. Similarly, in most European countries, the onset of the decline was in the 1970s, while most studies have tended to focus on the last two decades of the 20th century. [148,149,265-267]

Do countries experiencing more recently the onset of the decline phase of the CHD epidemics have the same trend drivers as countries with longstanding declines? In countries with long established decline phases, risk factors explain about two thirds of the observed decline, while evidence based treatments explain about one third. However, the adoption of effective treatments happened towards the end of the century, and even then, treatment uptake levels in countries with strong health care systems were disappointingly low.[265,268] Thus, bigger contributions from evidence based treatments are plausible in countries that started the decline phase of the CHD epidemic more recently, since the revolution in evidence base cardiology was firmly underway in the 1990s.

As I described earlier in this chapter, Poland is a key Central European country in which to study the abrupt changes in rates. Cardiovascular disease deaths increased steadily through the seventies and eighties, continuing to the very end of the communist era. The dramatic socioeconomic changes then occurred during the transition to a market economy were accompanied

by sharp falls in mortality from 1991 onwards -one of the fastest declines in the world- resulting in substantial improvements in life expectancy, mainly attributable to decreases in cardiovascular mortality.[269] Several countries in central Europe experienced equally dramatic political and socioeconomic changes in the nineties, including the Czech Republic, East Germany, Hungary and Romania.[270]

I have already discussed the Zatonsky/Willett hypothesis that this might be related to dietary changes, as a consequence of the elimination of subsidies for animal fats during the socialist era, resulting in a fall in the consumption of saturated fats, whilst the intakes of polyunsaturated fats, fruits and vegetables all increased following the introduction of a market economy.[187,252]

However, the potential contribution of treatments and other risk factors remains unclear. For instance, smoking prevalence in men also fell significantly during that period.[187,253] Indeed, changes in other cardiovascular risk factors might also have played a significant role on the observed mortality decline. Furthermore, improvements in evidence-based treatments for established coronary disease also became widely used in recent decades in Poland. This included therapies for acute myocardial infarction, CHD and heart failure, hypertension and hypercholesterolemia, as well as coronary bypass surgery, coronary angioplasty and stenting.

My aim was therefore to explain the contribution of risk factor changes and evidence based treatments in the recent fall in coronary mortality observed in Poland since 1990. Such an analysis is potentially important, both for understanding past trends and for planning future strategies.

6.3.2 Methods

To explain the changes in cardiovascular mortality in Poland between 1991 and 2005 we used the IMPACT CHD mortality model. This has been previously validated in the U.K., Italy, Sweden, Canada and the U.S.[144,149,267,271] A detailed description of the model methods and data source is available in appendix A2.

The model goal is to quantify what proportion of the coronary heart disease deaths prevented or postponed in the Polish population between 1991 and 2005 can be explained by risk factors and treatments. The model is comprehensive, incorporating all usual treatments for coronary heart disease and heart failure plus all major cardiovascular risk factors, including smoking, blood pressure, cholesterol, diabetes, obesity and physical activity.

All available Polish data sources were therefore systematically identified and critically reviewed as inputs in the Polish IMPACT model. The analysis was confined to adults aged between 25 and 74 years. Mortality and demographic data were taken from routine national statistics. Coronary heart disease patient numbers and treatments were obtained from cross-sectional national and local studies; country representative surveys (WOBASZ[258], NATPOL[260,261], Pol-MONICA[259]), national registries (CABG registry[257], acute coronary syndromes registry[255,256]) and hospital discharge databases. Expert opinions were also elicited where objective data were deficient. Data quantifying changes in the prevalence of cardiovascular risk factors were taken from national representatives surveys (NATPOL, WOBASZ,) as well as from the best regional and local epidemiological studies (Pol-MONICA and CINDI WHO[272]). More details on the data sources of the Polish IMPACT model are available in appendix A2.

Calculating the number of deaths prevented or postponed to be explained

Age and sex specific mortality rates for coronary heart disease were obtained from the Polish Central Statistical Office. Substantial changes in the coding of causes of death in Poland were introduced in 1997. I have discussed in section 6.2 the coding quality issues concerning polish cardiovascular mortality data for the period 1991-1996, and the data used was corrected for these issues with the approach developed by Jasisnki et al.[254]

The number of CHD deaths expected in 2005 if the 1991 mortality rates had persisted was then subtracted from the number of deaths actually observed in 2005 to produce the fall in mortality that the model needed to explain.

We then estimated the proportions of the total number of deaths prevented or postponed (DPPs) which could be attributed to the use of treatments and to changes in cardiovascular risk factors.

Estimating Treatment benefits

The treatment arm of the Model includes the following populations of patients:

-those hospitalized with an acute myocardial infarction (AMI),

-Patients admitted to the hospital with unstable angina,

-Community-dwelling patients who have survived an AMI,

-Patients who have undergone revascularisation procedure (coronary artery bypass grafting (CABG), or a percutaneous coronary intervention (PCI), with or without stent.

-Community-dwelling patients with angina pectoris (no revascularisation)

-Patients admitted to hospital with heart failure,

-Community-dwelling patients with heart failure (no hospital admission).

-Hypertensive individuals eligible for hypertensive therapy

-Hypercholesterolemia subjects eligible for cholesterol lowering therapy

For each of the groups, we estimated the number of DPPs that were attributable to various treatments. The size of each individual group was determined using data from hospital episodes statistics, disease registers and surveys (See appendix A2.)

Data on the clinical effectiveness of each intervention and therapy were based on the most recent meta-analyses and large randomized clinical trials. Details on the magnitude of the risk reduction for each treatment and its uptake are available in appendix A2

The number of deaths prevented or postponed as a result of each individual intervention in each group of CHD patients in the year 2005 was then calculated by multiplying the number of patients in each diagnostic group by their baseline case-fatality rate over 1 year, by the proportion of these patients receiving a specific treatment, and by the relative reduction in one–year case-fatality by the administered treatment.

For example, in Poland, in 2005, approximately 12 230 men aged 55-64 were hospitalized with acute myocardial infarction. Their expected age-specific 1-year case-fatality rate without treatment was approximately 5.4%. From registry data[256] 96% of them were given aspirin or other antiplatelet drugs, interventions with an expected mortality reduction of 15%. The number of deaths prevented or postponed for at least a year by the use of aspirin among men aged 55 to 64 were then calculated as:

[Eq 1] 12 230 x 0.054 x 0.96 x 0.15 = 95 fewer deaths

This process was then repeated for men and women in each age group, each patient group and each therapy. Some adjustments were made to these basic analyses. Many evidence-based

therapies were not used Poland in 1991 (e. g. statins, or primary angioplasty in acute myocardial infarction). However, in some cases the use of some drugs or procedures in 1991 was not negligible (for instance antihypertensive treatment or aspirin in acute myocardial infarction). In such cases, in order to obtain the net benefit, the number of deaths prevented or postponed as a result of the therapy as used in 1991 was calculated and subtracted from the number calculated for 2005.

Compliance, (adherence, the proportion of treated patients actually taking effective levels of medication), was assumed to be 100% among hospital patients, 70% among symptomatic community patients and 50% among asymptomatic community patients.[273] To avoid double counting of patients, it was necessary to identify potential overlaps between different groups of patients. For example, approximately half the patients having CABG surgery have a previous AMI[220], approximately 25% of AMI survivors develop heart failure within 12 months[274], and over 50% of CHD patients have a history of hypertension.[275]

To quantify the relative reduction in case-fatality rate for individual patients receiving multiple treatments, we used the conventional Mant and Hicks cumulative relative benefit approach[276]:

[Eq 2] Relative Benefit = 1 - [(1-relative reduction in case-fatality rate for treatment A) X (1-relative reduction in case-fatality rate for treatment B) X ... X (1- relative reduction in case-fatality rate for treatment N).

For example, considering appropriate treatments for AMI survivors, applying relative risk reductions (RRR) for aspirin, beta-blockers ACE inhibitors statins and rehabilitation then gives:

[Eq 3] Relative Benefit = 1 - [(1 –aspirin RRR) X (1 - beta-blockers RRR) X (1 - ACE inhibitors RRR) X (1- statins RRR) X (1- rehabilitation RRR)]

= 1 - [(1- 0.15) X (1-0.23) X (1-0.20) X (1- 0.22) X (1- 0.26)]

= 1 - [(0.85) X (0.77) X (0.80) X (0.78) X (0.74)]

= 0.70 i.e. a 70% lower case fatality

This represents a 34% relative reduction (0.70/1.06) on the simple additive value of 106%.

Risk factor changes and mortality benefits

We estimated the contribution of risk factors to the mortality decline by using two approached: the regression approach for continuous risk factors and the population attributable risk fraction approach for discrete risk factors.

Regression approach

Regression coefficients published in the literature were used to calculate the number of deaths prevented or postponed as result of change in systolic blood pressure, mean cholesterol concentration and body mass index (BMI). The number of deaths prevented and postponed due to change in that risk factor was then calculated as the product of the number of CHD deaths observed in the baseline year (1991), the change in risk factor level and the coefficient quantifying the change in CHD mortality per unit of absolute change in that risk factor.

For example, there were 2534 CHD deaths among women aged 55-64 years in 1991, the base year. Mean systolic blood pressure in this group decreased by 5.4 mmHg between 1991 and 2005. The largest meta-analysis demonstrates an age- and sex-specific reduction in mortality of 50 percent for every 20 mmHg reduction in systolic blood pressure, generating a logarithmic coefficient of –0.035[277]. The number of deaths prevented or postponed was then estimated as:

[Eq 4] [deaths in 1991] * (1-EXP(coefficient*change)

= 2534 (1-EXP(-0.035*5.4)) = 436 fewer deaths

Population attributable risk approach

A population attributable risk fraction approach was used to assess the effect of changes in the prevalence of smoking, diabetes and physical inactivity, using the standard formula:

[Eq 5] ((P x (RR-1)) / (1+P x (RR-1)) ,

Where P = prevalence of the risk factor and RR = the relative risk for CHD mortality associated with that risk factor.

To assess the decline in CHD mortality, the number of coronary heart disease deaths in 1991 (the base year) was multiplied by the difference between the population-attributable risk fraction in 1991 and that in 2005.

We assumed that there was no further synergy between the treatment and risk factor sections of the model, or between the major risk factors because the regression coefficients and relative risks for each risk factor were each independent, being obtained from multivariate analyses. Deaths prevented or postponed as a result of risk factor changes were then systematically quantified for each patient group. Lag times between risk factor rate change and event rate change were not modelled. We assumed, as in other countries, that any time lag would be relatively unimportant over a period of fifteen years (1991-2005).[278]

Model validation: comparison of estimated with observed mortality changes

The model produces estimates of the total number of CHD deaths prevented or postponed attributable to each treatment and to change in each specific risk factor. These estimates were then summed and compared with the observed changes in mortality for men and women in each specific age group. Any shortfall in the overall model estimate was then presumed to be attributable either to inaccuracies in our methodology or to other, unmeasured risk factors.

Sensitivity analyses

All the above assumptions were tested in a multi-way sensitivity analysis using the analysis of extremes method.[279] This method consist in choosing for each model parameter, a lower and upper value using 95% confidence intervals where available, or otherwise using + 20% values (for patient numbers, treatment uptake, and compliance), and then recalculating the model outputs using these "extremes" values.

An example of calculating lower and upper bound estimates for DPPs for treatment with aspirin among men aged 55-64 years who were hospitalized with an AMI is presented in Table 6-3.

We used 95% confidence intervals from the Antithrombotic Trialists' Collaboration meta-analysis[280] for relative mortality reduction; lower and upper bound estimates for the other parameters were calculated as minus or plus 20% [except for treatment uptake that was capped at 99%]. Multiplying all the lower-bound estimates yielded the minimum [lower bound] estimate and multiplying the upper-bound estimates yielded the maximum [upper bound] estimate.

This approach may be described as a "robust" for two reasons.

a) Maximum and minimum values for each variable were deliberately forced to provide a wider range rather than a narrower one, e.g. relative mortality reduction +20% rather than say, +10%.

b) The resulting product, for instance the minimum estimate, was generated by assuming that the lowest feasible values all occurred at the same time, a most unlikely situation.

Table 6-3. Example of sensitivity analysis

	Patient numbers	Treatment Uptake	Relative Mortality Reduction*	One year case fatality	Deaths prevented or postponed
	A	***B***	***C***	***D***	***(A x B x C x D)***
Best Estimate	12 226	0.96	0.15	0.054	95
Minimum estimate	9 781	0.77	11%*	0.043	36
Maximum estimate	14671	0.99	19%*	0.065	179

* 95% CI from the Antithrombotic Trialists' Collaboration meta-analysis[280]

6.3.3 Results

The large decline in CHD mortality rates since 1991 resulted in 26 200 fewer CHD deaths in 2005. The model explained approximately 23 715 (91%) of this mortality decrease.

Approximately 37% of the mortality fall was attributable to treatments and approximately 54% was attributable to changes in risk factors. A good agreement between estimated and observed number of deaths was generally observed across all gender and age groups. However, in middle aged men, the number of predicted deaths prevented or postponed was underestimated.

Medical and surgical treatments

Estimated numbers of CHD deaths prevented or postponed by medical and surgical treatment in 2005 are presented in Table 6-4. All treatments accounted for approximately 9 640 fewer deaths, representing approximately 37% of the mortality decrease.

The largest reductions came from heart failure treatments in hospital and in the community, which resulted in approximately 3100 fewer deaths in 2005 (12% of the observed mortality

reduction). Initial treatments for acute myocardial infarction or unstable angina (generated approximately 2450 fewer deaths, 9% of the observed fall). Secondary prevention therapies after myocardial infarction or revascularization explained approximately 1930 (7%) fewer deaths, followed by chronic angina treatments some 710 (3%), hypertension treatments approximately 580 (2%) and statins for hypercholesterolemia in primary prevention some 880 (3%) fewer deaths.

Risk factor changes

Estimated numbers of CHD deaths prevented or postponed by changes in the exposure to risk factors are presented in Table 6-5. Approximately 14,070 of the CHD deaths prevented or postponed (54%) were attributable to changes in risk factors, of which the majority, (41% of the fall in men and 33% in women) was attributable to large decreases in mean cholesterol concentration (declining by 0.4 mmol/L).

The effects of changes in smoking and mean blood pressure in men and women were more complex. Smoking prevalence decreased in men by 15.7% explaining approximately 15% of their mortality fall. In women very little change in smoking prevalence was observed, which thus had virtually no effect on CHD mortality. Mean systolic blood pressure fell by 2.7 mmHg in men and by 5.2 mmHg in women. After subtracting the effects of hypertension treatments, these blood pressure falls explained approximately 29% of the mortality decrease in women and an 8% increase in deaths in men. Increased leisure time physical activity explained approximately 10% of the decrease in deaths in the Polish population.

However, these gains were partially offset by approximately 1810 additional deaths attributable to increases in body mass index (-4% and -5% for men and women respectively) and increasing diabetes prevalence (-1% and -8% respectively).

Sensitivity Analysis

Under the assumptions of the sensitivity analysis, the relative contributions of specific risk factor changes and treatment effects remained similar. The extreme minimum and maximum numbers of CHD deaths prevented or postponed were 14 050 (54%) and 36 840 (141%) of the observed mortality fall.

Table 6-4 Estimated coronary heart disease deaths prevented or postponed by medical and surgical treatments in Poland in 2005

Patient groups & specific treatments§	Patients Eligible†	Deaths Prevented or Postponed					
		Number †			% of total mortality fall§		
		Best estimate	Minimum	Maximum	Best estimate	Minimum	Maximum
Acute myocardial infarction	52 180	1 340	370	2 550	5.1	1.4	9.7
Unstable angina	105 920	1 110	550	1 850	4.2	2.1	7.1
Secondary prevention post-myocardial infarction	213 970	1 300	520	2 650	4.9	2	10.1
Secondary prevention post-CABG/PCI	100 890	630	260	1 310	2.4	1	5
Chronic angina	706 670	710	300	1 510	2.7	1.1	5.8
Heart failure with hospital admission	18 330	1 470	700	3 550	5.6	2.7	13.6
Heart failure in the community	122 680	1 630	730	3 760	6.2	2.8	14.4
Hypertension treatments	8 488 520	580	-440	1 260	2.2	-1.7	4.8
Statins for primary prevention lipid reduction	14 046 930	880	360	1 830	3.4	1.4	7
Total Treatments		9 640	3 350	20 270	36.8	12.8	77.5

†reported numbers are rounded to nearest 10.

§may not sum to total due to rounding.

Table 6-5 Estimated coronary deaths prevented or postponed as a result of risk factor changes in men and women in Poland 1991 - 2005

Population risk factor		Absolute level of risk factor		Change in risk factor		Beta regression coefficient	RR	Deaths Prevented or Postponed					
								Number of deaths†			Percent of total reduction‡		
		1991	2005	Absolute change	Relative change (%)			Best estimate§	Min§	Max§	Best % Estimate	Min %	Max %
Smoking prevalence (%)	men	55.8	40.1	-15.7	-28		3.1	2980	2390	3580	15%	12%	18%
	women	28.1	25.1	-3	-4		4.2	-10	-10	-10	0%	0%	0%
Systolic blood pressure	men	140.1	137.4	-2.7	-1.8	-0.034		-1720	-1250	-2380	-8%	-1%	-12%
	women	136.6	131.5	-5.2	-3.4	-0.042		1690	1100	2360	29%	19%	40%
Total cholesterol (mmol/l)§§	men	5.6	5.2	-0.4	-8.6	-0.95		8390	6010	10340	41%	29%	51%
	women	5.6	5.2	-0.4	-7.6	-0.91		1920	1440	2200	33%	25%	38%
Physical inactivity (%)	men	64.6	38.7	-25.9	-40.1		1.29	2000	1600	2400	10%	8%	12%
	women	68.8	44.5	-24.3	-35.3		1.35	630	510	760	11%	9%	13%
Body mass index (kg/m2)	men	26	26.9	0.9	3.2	0.03		-870	-480	-1340	-4%	-2%	-7%
	women	25.7	26.6	0.9	3.2	0.027		-290	-160	-450	-5%	-3%	-8%
Diabetes prevalence (%)	men	2.9	3.3	0.4	12.7		2.47	-190	-130	-250	-1%	-1%	-1%
	women	3.3	4.2	0.9	28.5		3.4	-460	-310	-630	-8%	-5%	-11%
Total risk factors	Men							10 600	8130	12340	52%	40%	61%
	Women							3 480	2570	4230	60%	44%	73%

RR: relative risk §antihypertensive treatment effects subtracted
†reported numbers are rounded to nearest 10. ‡ may not sum to total due to rounding.
§§ statin effects subtracted.

6.3.4 Interpretation

There were 26,200 fewer coronary deaths in Poland in 2005 compared with 1991, approximately 55% being attributable to beneficial changes in risk factors and 37% to the increased use of evidence-based treatments.

The major contributors to the mortality fall were large falls in total cholesterol, plus beneficial reductions in systolic blood pressure in women and decreased smoking in men. Physical activity also contributed to the decline in deaths. Worryingly, adverse trends negated some of these benefits, specifically increases in the prevalence of obesity, diabetes and blood pressure levels in men and smoking prevalence in women.

The most important treatment contributions came from therapies for heart failure, angina and secondary prevention.

This is the first time the Impact model has been utilized in Central Europe, where many countries experienced a rapid decline in CHD mortality after the transition to a market economy. These included the Czech Republic, Slovakia, Hungary, East Germany and Romania. In contrast, mortality trends fluctuated in some other former communist countries that experienced more complicated pattern of mortality trends after the fall of communism, like Russia and Ukraine. For example in Russia, mortality initially fell rapidly for the first few years after the collapse of the former Soviet Union, but then began to rise following the economic crisis in 1998.[281] Interestingly, the explanation for these more complex mortality trends is currently attributed to increases in heavy alcohol intake[99,100], however, a more exhaustive analysis of trend drivers has not been conducted.

The IMPACT model is a comprehensive tool that can quantify changes in mortality as a function of improving therapies and the major “downstream” risk factors (smoking, cholesterol level, blood pressure, obesity, diabetes and inactivity). Four of these six major risk factors reflect dietary habits; these in turn are powerfully patterned by “upstream” political and socio-economic factors. In our analyses, we observed a powerful effect of diet-related changes in cholesterol level on coronary heart disease mortality among both men and women. This is consistent with the earlier hypothesis that favourable dietary changes during the socio-political transition[252,253] were the main reason for the sharp decline in cardiovascular mortality, changes that have been sustained throughout the period studied with the IMPACT model. In contrast, statins made a surprisingly small contribution to the overall cholesterol reduction.

Between 1991 and 2005, systolic blood pressure decreased substantially in women and young men; but increased in men aged over 55 years. This trend was consistently observed in three different sets of contemporary local and national studies. It generated over 1000 additional coronary deaths. However, it remains unclear why such important and worrying sex differences in blood pressure trends occurred. More research is needed, particularly around possible gender and socio-economic differences in the intake of salt and other dietary factors.

Increased physical activity resulted in some 2500 fewer coronary deaths. The main benefits came from increases in leisure time physical activity in Poland and are now well documented.[282,283]

The uptake of evidence-based treatments for coronary heart disease increased markedly, mirroring other developed countries. However, these pharmacological therapies and invasive procedures together explained barely one third of the mortality decrease (37%). This reflects a dynamic development in clinical cardiology in Poland in the late 20th century. Several new centres of invasive cardiology were created during this period demonstrating medical standards comparable to those in Western countries. However, at the start of the period, when the mortality trend started to change its direction, the level of uptake of most treatments was extremely low, suggesting that at that particular point in time, their contribution was even smaller. For example, the modern management of heart failure made the single biggest treatment contribution to the reduction in CHD mortality (12%). However angiotensin-converting enzyme inhibitors (ACEIs) uptake levels in the first half of the period were very low, and spironolactone was only introduced around the year 1999 with the RALES study,[284] Therefore it seems plausible that most of the deaths prevented were actually achieved during the second half of the 20 year period, when the epidemic was already in a sustained decline phase. Although revascularization was available throughout the period, the mortality impact of invasive cardiology was modest (barely 4%). This suggest that risk factors changes at the start of the decline phase were more critical determinants of the trend

This analysis is the first complex and quantitative analysis of the causes of sharp mortality fall in country experiencing a rapid transition from communism to democracy and market economy. The IMPACT model is comprehensive, and takes into account all known important downstream risk factors and all standard treatments. The model has been previously validated in many Western countries and its results are consistent with other analyses performed in the same settings.

Several limitations should also be noted. In Poland, data for the initial analysis year (1991) was less complete and representative than in subsequent years. The model failed to explain 9% of the

overall reduction in CHD deaths: residual confounding in many of the risk factor effect estimates is likely and, furthermore, the model does not quantify all potential risk factors (e.g. psychosocial).[27]

Our model results are generally consistent with other analyses conducted in Western Europe, the US and elsewhere. However, interesting differences do exist. Thus, the contribution from population risk factor changes was even bigger in Nordic countries, probably reflecting more effective health policies at national and local levels.[196] In contrast, in the UK, large reductions in smoking prevalence since 1980 had a large impact on reducing mortality whereas the dietary changes were far more modest.[149]

6.4 CONCLUSIONS

In conclusion, coronary heart disease deaths in Poland plummeted after 1990. Over half of the recent mortality reduction was associated with favourable changes in exposure to major risk factors, while approximately one third was attributable to modern therapies, probably acting towards the end of the study period.

These results demonstrate the powerful effect of moderate changes in population level risk factors on CHD mortality. The positive trends in risk factors most probably reflect beneficial changes in food prices and accessibility following economic transformation. These benefits were substantially greater than those from recent improvements in healthcare systems and medical therapy. Crucially, all these changes happened in a very abrupt way and with almost no lag time in relation to the fall in mortality (see section 6.2).

The rapid decline phase of the coronary heart disease epidemic in Poland is thus mainly attributable to decreases in major risk factors that can be linked to the substantial changes in dietary factors “forced” in the population during the socio-political transition to a democracy and a market economy. The “natural experiment” which occurred in Poland now requires further support from evidence-based policy interventions. Furthermore, these analyses have implications for strategies to fight future epidemics of CHD. Effective legislation to control smoking, dietary salt and saturated fat consumption could be rapidly beneficial.

Poland seems to have achieved a substantial socioeconomic transformation with only modest increases in inequalities. In both Poland and Hungary, all cause mortality rates decreased or

remained the same in all educational groups between 1990 and 2000; in Estonia and Lithuania, those with lower educational levels showed higher mortality, mainly attributable to cardiovascular disease and external causes.[263] However, data on CHD mortality and risk factors trends is lacking for these latter countries, preventing further analysis of this crucial aspect.

Substantial socio-economic inequalities exist in most developed countries. Intriguingly, many of these countries are showing evidence of slower pace of change in coronary heart disease mortality, after several decades of solid decline.

Because of the social patterning of risk factors, differences in the pace of decline of CHD mortality trends by socio-economic status might further support the role of risk factors as the main driver behind the trend patterns. However, this is extremely difficult to study because few countries have detailed mortality, risk factors and treatment trends by measure of socioeconomic level. An exception in this regard is the UK.

In the next chapter, I will therefore further examine potential socio-economic differences in mortality trends in Scotland and in England, both being countries demonstrating substantial inequalities and large coronary heart disease burdens.

Thereafter, I will use an extended version of the IMPACT model to formally explore any socioeconomic differences potentially underlying these trends.

7 CHD MORTALITY TRENDS IN SCOTLAND AND ENGLAND BY SOCIOECONOMIC STATUS

7.1 INTRODUCTION

I have discussed in chapters 3 and 4 the role of risk factors in explaining CHD mortality rates. Furthermore, I also described the existence of important socioeconomic gradients in coronary heart disease burden and in the distribution of risk factors. In Chapter 6, I discussed how Poland experienced a rapid decline in CHD mortality with relatively modest increases in inequalities, and with risk factors playing a major role.

The known social patterning of risk factors suggests that any change in risk factors that show socioeconomic differentials should result in trend changes with similar socio-economic characteristics. However, the causal web linking socio-economic circumstances and cardiovascular disease outcome is complex, and predicting the effects on mortality trends is therefore correspondingly more difficult. This is a very difficult topic to study, as data are very sparse. However, the UK situation in this respect is privileged and substantial work on the association of social determinants and CVD outcome has been undertaken in this country.

In this chapter, I will analyse trends from two UK countries (first Scotland and then England), where data on CHD mortality trends by socioeconomic status are available. I will also use an extended version of the IMPACT model which takes into account socio-economic status, to further explore trend determinants in the English population.

7.2 RECENT LEVELLING OF CORONARY HEART DISEASE MORTALITY RATES AMONG YOUNG ADULTS IN SCOTLAND MAY REFLECT MAJOR SOCIAL INEQUALITIES

7.2.1 Introduction

Scotland has seen a halving of coronary heart disease mortality in the last two decades. [285] However, this country still experiences some of the highest CHD mortality rates in Europe and globally .[286]

In other countries with high but declining coronary heart disease mortality rates, several reports suggest that these trends may be changing. [189,192,227,231] Slowing or flattening of coronary heart disease mortality rates in young adults seems to recently happened in England & Wales, United States [192] Australia, the Netherlands and New Zealand.[227] The pattern for major cardiovascular risk factor trends is also changing, with dramatic increases in obesity and diabetes in all industrialised countries[287], flattening of blood pressure falls in US women[288], and persistent smoking in young adults in the United Kingdom and elsewhere. [289]

Recent trends in cardiovascular risk factors among Scottish adults present a correspondingly complex picture. There was significant progress between 1997 and 2003, with decreases in physical inactivity, dietary intake of fat, salt, and smoking [which reached government targets sets for 2010].[290] However, recent and substantial increases in obesity and diabetes, particularly among young adults, raise concerns about adverse effects on their subsequent coronary heart disease mortality rates. [291]

Because most cardiovascular risk factors are powerfully associated with socio-economic deprivation[292], I hypothesized that if there were any deterioration in mortality rates in the young, this might be seen particularly in those most materially deprived. I therefore examined recent trends and social inequalities in age-specific coronary heart disease mortality rates in Scotland, particularly among disadvantaged younger adults.

7.2.2 Methods

Mortality statistics

Vital statistics data were obtained for the Scottish population for the period 1986-2006. We limited our analyses to people aged 35 years and older. The underlying cause of death from coronary

heart disease was determined using the International Classification of Diseases (ICD)-9 codes 410-414 for 1986-1998 and ICD-10 codes I20-I25 for 1999-2006.

Age-adjustment was performed using the direct method , using the European standard population as reference.[293]

Socio-economic status data

Area level socio-economic status was categorized using the Scottish Index of Multiple Deprivation (SIMD) 2006 quintiles. The SIMD is the official Scottish Executive measure of area based multiple deprivation. It is based on 31 indicators in six individual domains [current income, employment, housing, health, education, skills and training and geographic access to services and telecommunications]. SIMD is calculated at data zone level (median population size of 770), enabling small pockets of deprivation to be identified. The data zones are ranked from most deprived (1) to least deprived (6505) on the overall SIMD index. The result is a detailed and comprehensive picture of relative area deprivation across Scotland. SIMD is reported here using quintiles, being the first and second quintile the least deprived and the fourth and fifth the most deprived. [294] Since the SIMD health domain for 2000-2004 includes a mortality indicator, the Comparative Mortality Factor (CMF), this risks a tautology. We therefore repeated our analyses using only the income component of the SIMD index.

We then obtained data on coronary heart disease mortality by age and sex for the period 1986-2006, and SIMD data for the period 1996-2006.

Trend Analysis

Plots of rates and plots of annual absolute changes in the age-specific mortality rates were smoothed using 3-year moving averages. A Joinpoint regression was fitted to provide estimated annual percentage change and to detect points in time where significant changes in the trends occur (JOINPOINT software version 3.0)[209]. A Bayesian Information Criterion (BIC) approach was used to select the most parsimonious model that fits best the data. A maximum number of three joinpoints was allowed for estimations. For each annual percentage change estimate, we also calculated the corresponding 95% confidence interval (95% CI). We performed two Joinpoint regression analyses. The first covering the period 1986-2006 for age and sex specific coronary heart disease mortality rates alone; and the second covering the period 1996-2006, for sex, age and deprivation specific coronary heart disease mortality rates, (the period was chosen because limited data on deprivation). To increase statistical power for these latter analyses, we then combined the deprivation data into

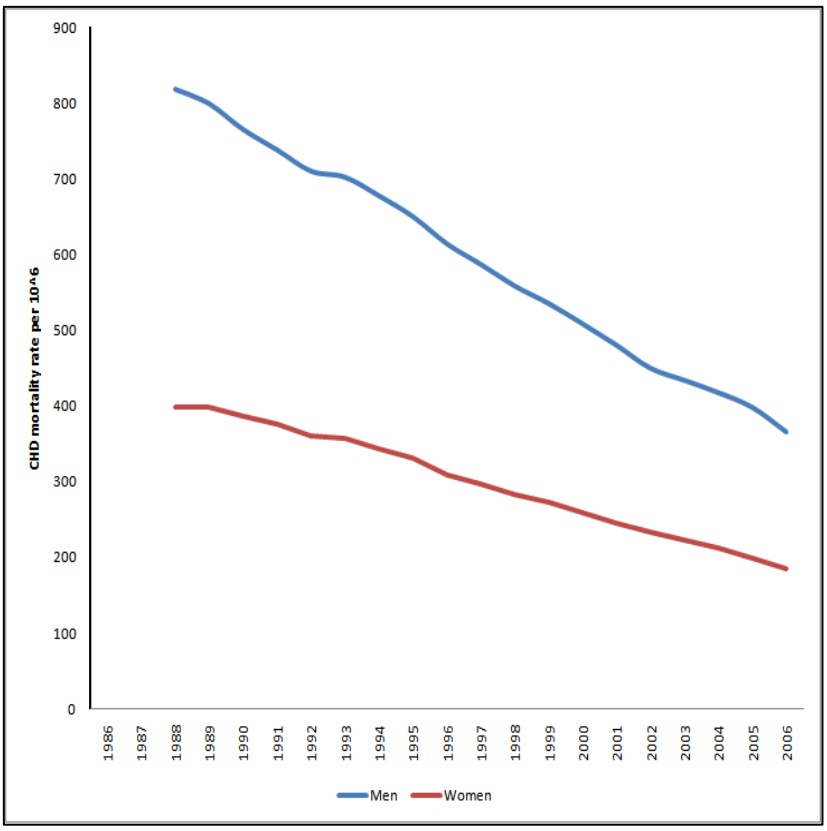
three groups: the two most deprived quintiles (3 & 5), the intermediate quintile (3) and the two least deprived quintiles (1 & 2).

7.2.3 Results

Age adjusted coronary heart disease mortality trends

Between 1986 and 2006, the age-adjusted coronary heart disease mortality rates decreased overall by 60.9% in men and by 56.4% in women (Figure 7-1). The average rate of decline in men was -2.88% (95% CI -3.86% to -1.89%) from 1986 to 1993, and for the period 1993-2006, -5.03% (95%CI -5.40% to -4.65%). For women, the average rate of decline was -2.23% (95%CI -3.11% to -1.34%) in the period 1986-1993 and -5.04% (-5.37% to -4.70%).for 1993-2006.

Figure 7-1 Age standardized coronary heart disease mortality rates in Scotland by gender, 1986-2006



Age and sex specific coronary heart disease mortality trends

Age specific rates revealed a more complex picture (Figure 7-2).

Furthermore, the APC between 2004 and 2006 was not significantly different from 0, [point estimate for the APC +6.4%, -6.72 to 21.38 (Table 7-2].

In men and women aged up to 75 years, the APC was consistently smaller in the most deprived quintiles compared with the most affluent (Table 7-2 and 7-3). Similar results were observed when the analyses were repeated using the SIMD income component alone.

Figure 7-2 Age specific coronary heart disease mortality trends (Scotland 1986-2006, men and women).

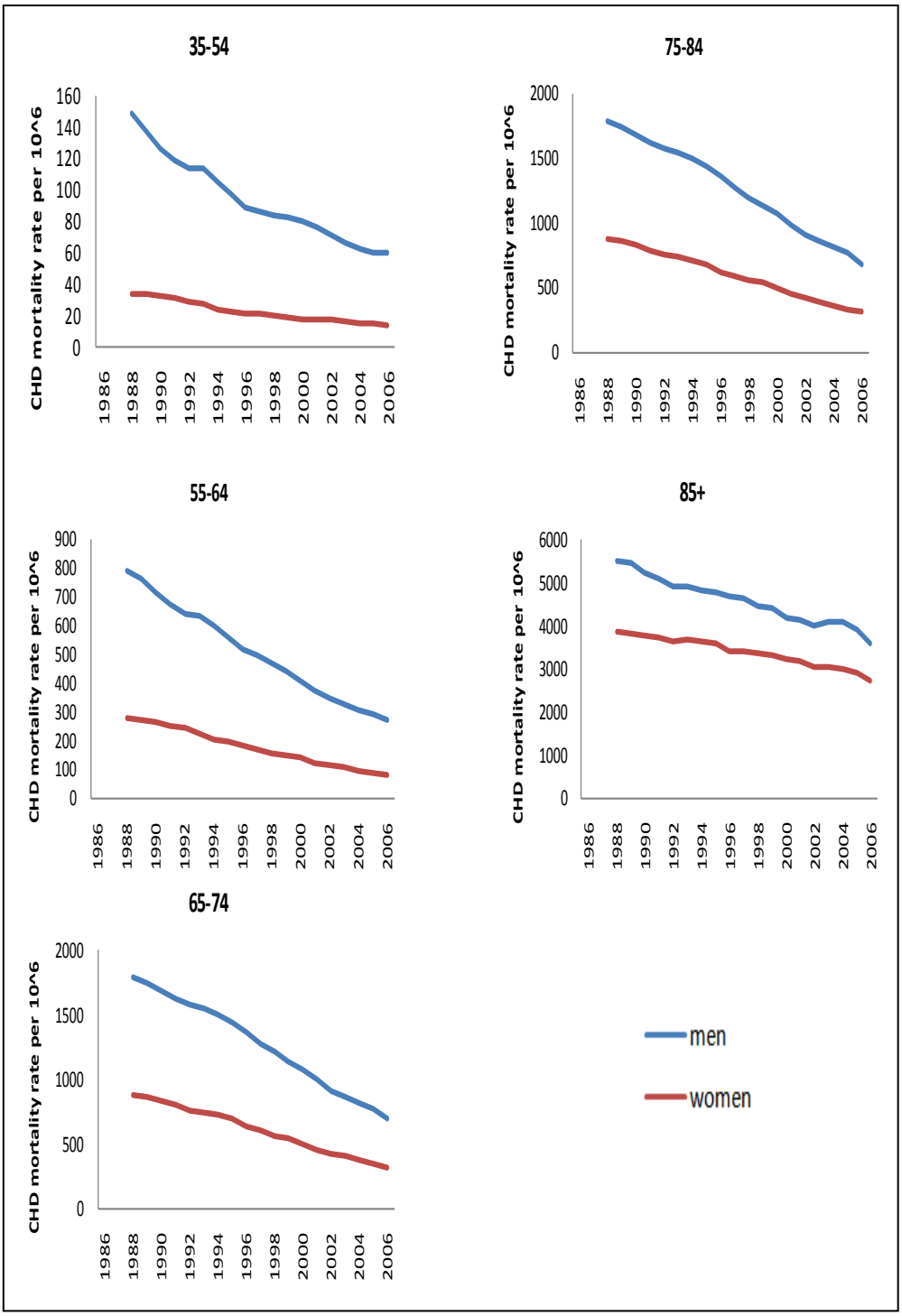


Table 7-1 Coronary heart disease mortality trends in Scotland 1986-2006: Joinpoint analysis in men and women aged over 35years

Age group [years]	Periods	Deaths, number	Rates* (min-max)	EAPC	95%CI	Periods	Number of deaths	Rates** (min-max)	EAPC	95%CI
	Men					Women				
35-54	1986 - 2003	434-955	60.3-157	-6.28*	-6.76 to -5.80	1986 - 1989	197-223	31.5-35.6	0.14	-6.96 to 7.78
	2003 - 2006	425-449	58.6-61.7	-0.55	-9.47 to 9.24	1989 - 1995	139-198	20.3-30.6	-9.02*	-12.31 to -5.60
						1995 - 2006	102-154	13.2-21.8	-4.94*	-6.24 to -3.61
55-64	1986 - 1997	1227-2152	483-826	-4.78*	-5.35 to -4.22	1986 - 1991	722-807	254-280	-2	-4.00 to 0.03
	1997 - 2006	743-1129	244-439	-8.81*	-9.82 to -7.78	1991 - 1999	387-612	137-217	-6.99*	-8.37 to -5.60
						1999 - 2006	245-369	78-130	-9.79*	-11.59 to -7.95
65-74	1986 - 1993	3003-3380	1523-1833	-3.72*	-4.57 to -2.86	1986 - 1989	2127-2258	851-899	-1.28	-4.2 to 2.49
	1993 - 1999	2190-2916	1106-1455	-5.54*	-7.13 to -3.92	1989 - 1998	1342-1947	542-785	-4.81*	-5.70 to -3.92
	1999 - 2006	1248-1946	599-978	-7.89*	-9.08 to -6.68	1998 - 2006	724-1253	293-509	-7.38*	-8.52 to -6.24
75-84	1986 - 1994	2835-2967	2763-3263	-1.77*	-2.74 to -0.79	1986 - 1993	3047-3477	1830-2055	-0.27	-1.38 to 0.84
	1994 - 2006	1692-1627	1492-2717	-6.59*	-7.20 to -5.97	1993 - 2006	1560-2738	898-1706	-5.42*	-5.92 to -4.92
85+	1986 - 1998	710-941	4123-5696	-6.52*	-7.16 to -5.86	1986 - 1998	1735-2200	3245-3913	-4.28*	-4.82 to -3.75
	1998 - 2003	890-992	3931-4508	-2.21	-6.09 to 1.83	1998 - 2003	1936-2177	3039-3394	-1.25	-4.36 to 1.97
	2003 - 2006	895-918	895-3989	-11.14*	-17.10 to -4.74	2003 - 2006	1756-1818	2581-2921	-6.76*	-11.72 to -1.52

EAPC: annual percent change. *EAPC significantly different from 0%. ** rates per 100000

In both men and women aged over 55, the annual percent rate change increased from 1986 to 2006. However, in men and women under 55, there were clear decreases in the annual percent change [APC]. Men aged 35-54 years showed recent, significant flattening of the trend since 2003. Furthermore, the APC for that period, -0.55% [95% CI -9.47 to +9.24] was not significantly different from 0%. (Table 7-1)

Likewise in women aged 35-54, the APC was -9.02% from 1989-1995 decreasing to -4.94% from 1995-2006, suggesting that the rate of decline is slowing down significantly in young women %. (Table 7-1)

Socioeconomic differentials in coronary heart disease mortality trends

Six-fold socio-economic differentials were observed between coronary heart disease mortality rates in the most deprived and most affluent quintiles in the youngest groups (Figure 7-3) although these differences were smaller in older age groups and disappeared above 85years. (Figure 7-5 and 7-6)

Age-standardized mortality rates across most deprivation quintiles decreased between 1996 and 2006 (Figure 7-3). However, there was no narrowing of the relative inequality gap (Figure 7-4). Coronary heart disease mortality rates in men aged 35-54 in the two most deprived quintiles decreased between 1996 and 2004 [APC -5.62%, -6.88 to -4.34].

Figure 7-3 Differences in coronary heart disease mortality trends by deprivation and gender, Scotland 1996-2006 (age standardised rates).

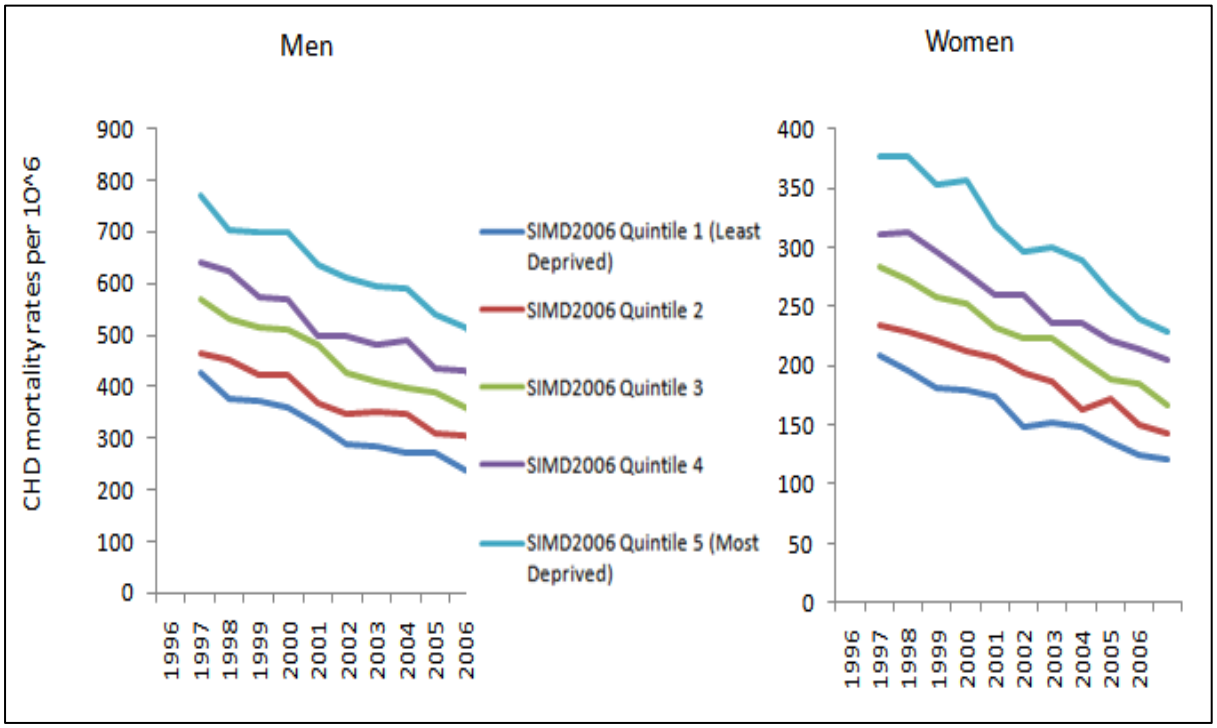


Figure 7-4 Trends in coronary heart disease death deprivation rate ratios (European standardized), Scotland 1996-2006, both genders. (Reference category is the 3rd quintile)

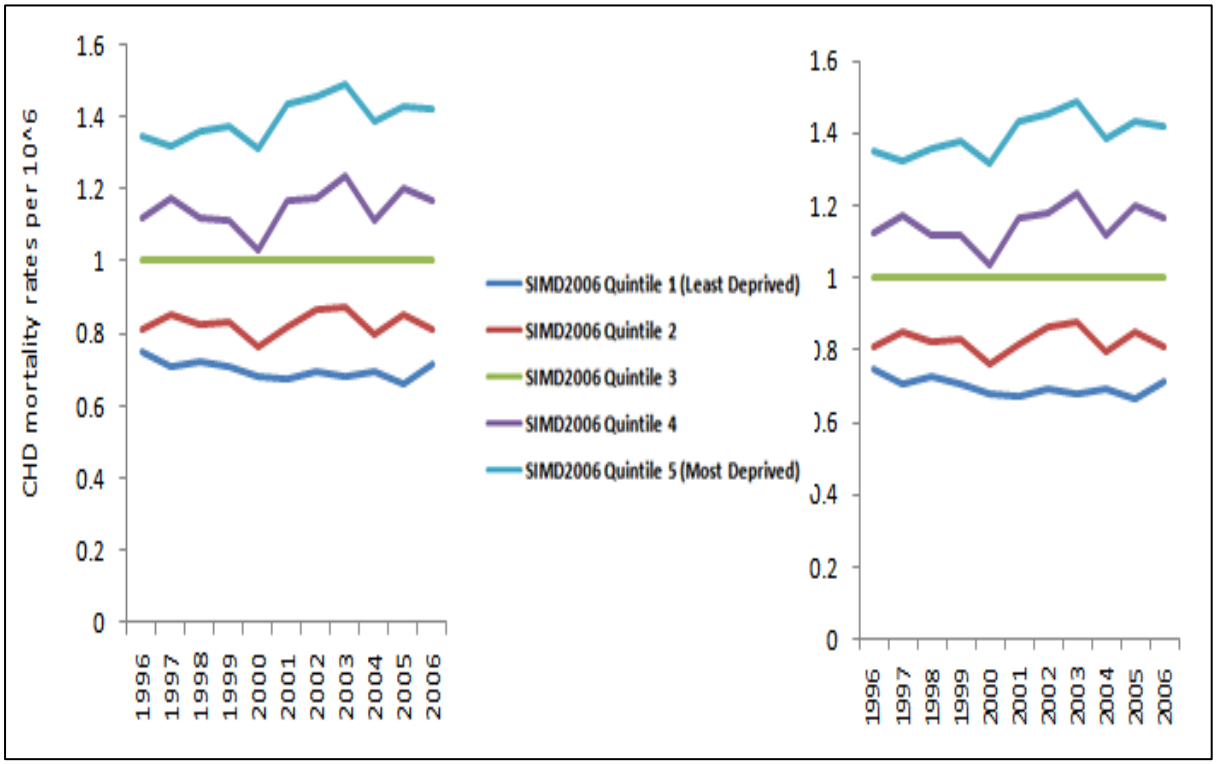


Figure 7-5 Coronary heart disease mortality trends by age and deprivation (Scotland 1996-2006, men).

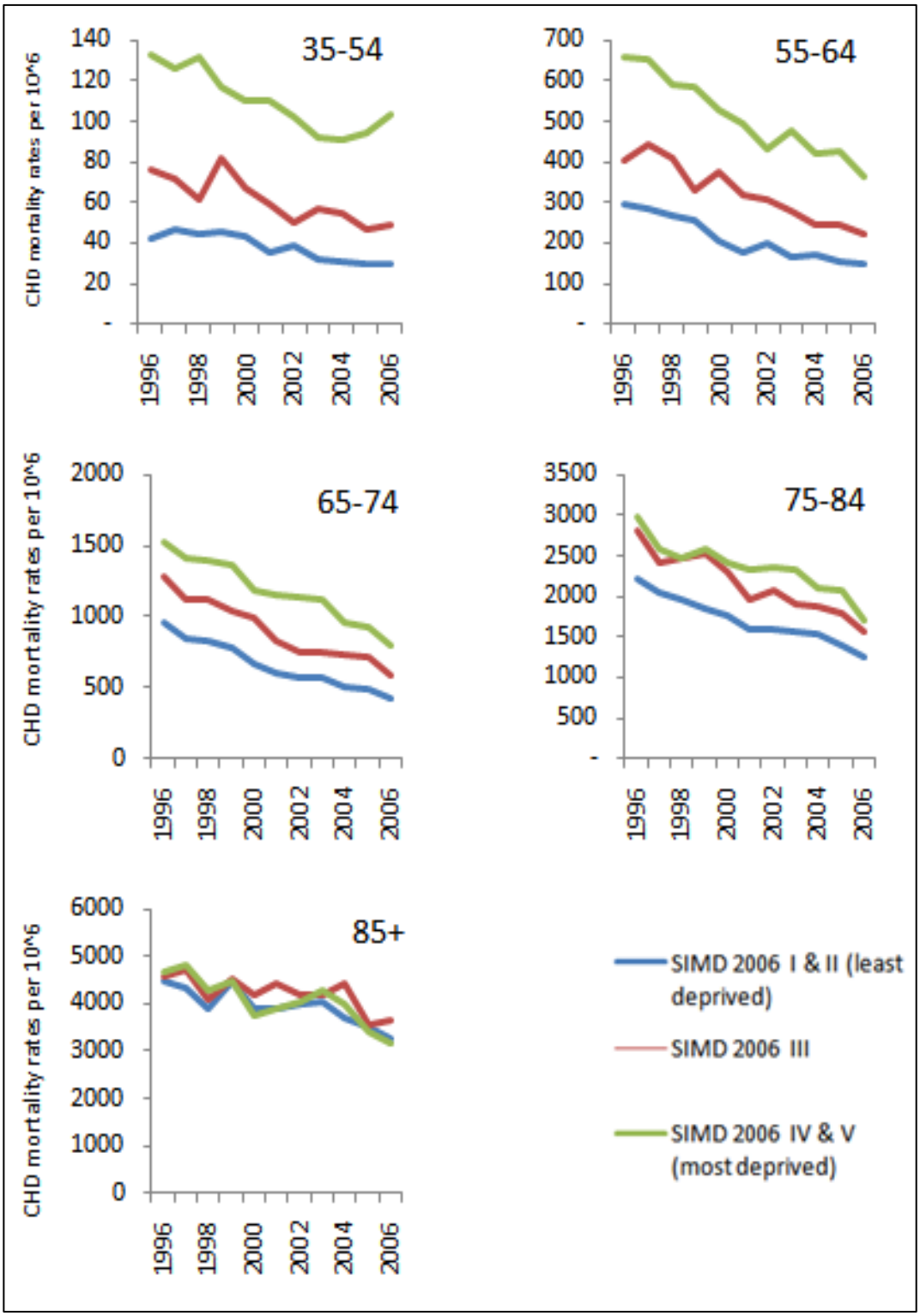
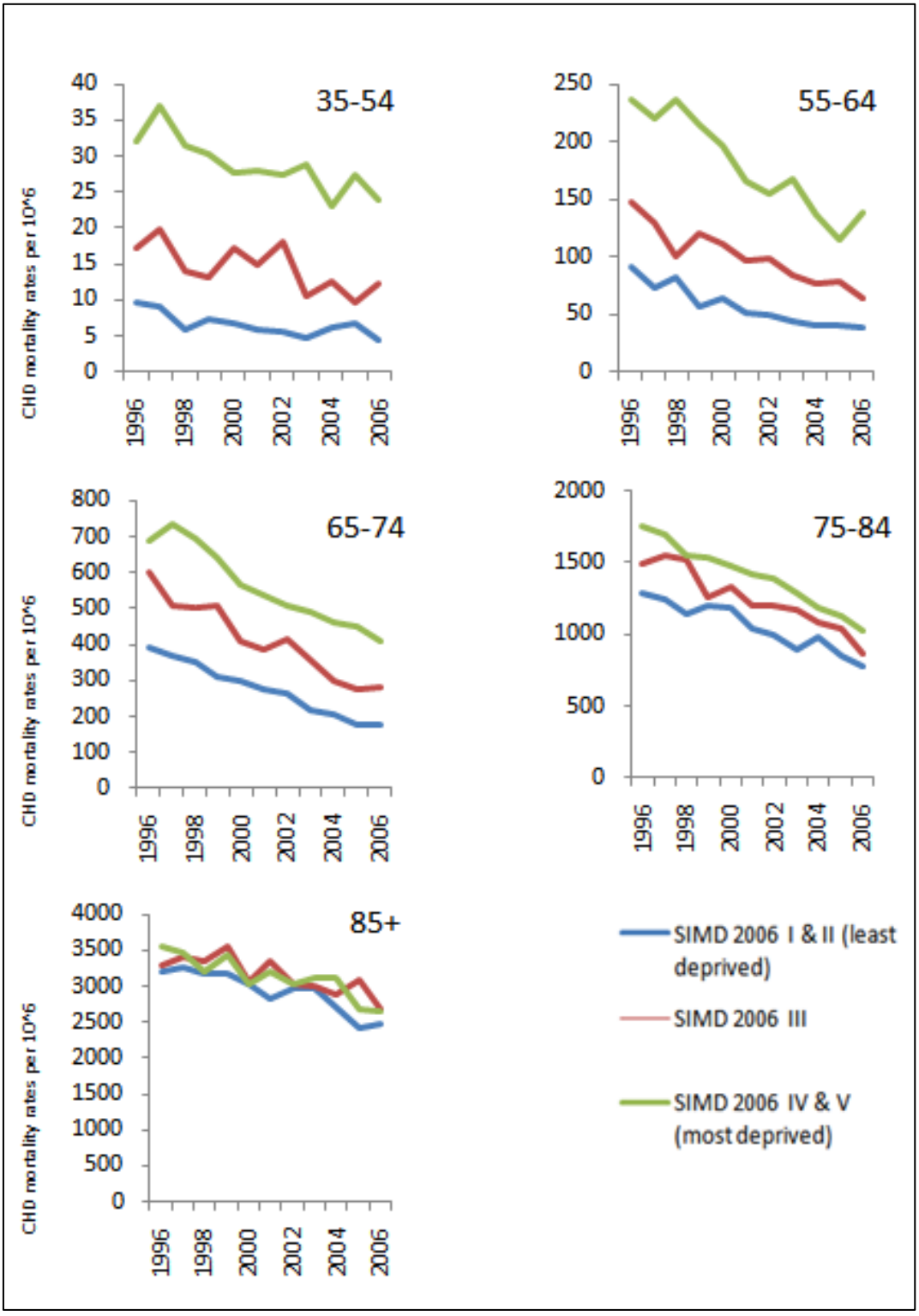


Figure 7-6 Coronary heart disease mortality trends by age and deprivation (Scotland 1996-2006, women)



7.2.4 Interpretation

The overall decline in age standardized CHD mortality rates conceals a flattening in younger men and women in Scotland, England and Wales and the USA. Furthermore, in Scotland between 1996 and 2006, the rate of decline in young men and women aged under 54 years, was significantly slower in the most deprived groups.

Moreover, substantial socio-economic differences in coronary heart disease mortality rates were seen in Scotland between 1986 and 2005. Social gradients were visible in all age groups up to the age of 85 years.

This analysis has several strengths. The Joinpoint regression analysis is able to identify periods of similar annual percent changes; this avoids the need to pre-specify periods (which may then bias the way in which the trends are analysed). Moreover, because the maximum numbers of possible join points was deliberately limited in this study, each annual percent change estimate was based on more data points.

However, such analyses also possess limitations. Since most of the trend changes were recent, the confidence intervals for their average annual percent changes were correspondingly wider. It is therefore important not to overstate the significance of these changes. The point estimate suggests an increase in young men. However, the wide confidence interval encompassing zero simply means that a flat line is possible or even a decline, albeit at a slower pace. This potentially important observation needs to be confirmed in other populations. Similar constraints apply when comparing rates of decline between social groups.

Although the data quality for mortality registration can't be assumed perfect, the potential for disproportionate miscoding of mortality in deprived areas over a short time appears very unlikely. Furthermore, a number of studies suggest that coding in coronary heart disease is good quality in the young, extending up to and beyond the age of 65 years.[295-297]

Table 7-2 Joinpoint analysis of coronary heart disease mortality trends by age and deprivation in Scotland 1996-2006: Men aged over 35years

Age group [years]	Deprivation Category	periods	deaths, number (min-max)	Rates (min-max)	EAPC	95% CI for EAPC
35-54	1&2 (Most Affluent)	1996 - 1998	50-82	33-57	2.47	-14.87 to 23.35
		1998 - 2006	39-83	25-57	-6.46*	-8.53 to -4.34
	3	1996 - 2006	69-116	47-82	-5.64*	-7.80 to -3.42
	4 & 5 (Most Deprived)	1996 - 2004	87-210	65-167	-5.62*	-6.88 to -4.34
		2004 - 2006	103-158	75-123	6.4	-6.72 to 21.38
55-64	1&2 (Most Affluent)	1996 - 2006	72-152	131-313	-10.44*	-11.59 to -9.27
	3	1996 - 2006	145-233	225-442	-9.65*	-11.26 to -8.01
	4 & 5 (Most Deprived)	1996 - 2006	170-455	295-803	-5.58*	-6.51 to -4.65
65-74	1&2 (Most Affluent)	1996 - 2006	143-376	368-1028	-9.43*	-10.24 to -8.62
	3	1996 - 2006	261-532	583-1279	-7.69*	-8.79 to -6.59
	4&5 (Most Deprived)	1996 - 2003	411-704	959-1610	-3.98*	-5.59 to -2.33
		2003 - 2006	309-430	727-1075	-8.58*	-15.43 to -1.18
75-84	1&2 (Most Affluent)	1996 - 2006	250-402	1204-2247	-8.29*	-8.78 to -7.80
	3	1996 - 2006	373-560	1550-2804	-6.83*	-7.94 to -5.72
	4&5 (Most Deprived)	1996 - 2006	366-603	1646-3080	-4.63*	-5.75 to -3.50
85+	1&2 (Most Affluent)	1996 - 2004	144-214	3467-4658	-4.30*	-6.43 to -2.12
		2004 - 2006	162-200	3164-3688	-13.3	-31.12 to 9.13
	3	1996 - 1998	187-207	4081-4698	-8.66	-24.09 to 9.90
		1998 - 2004	203-218	4166-4545	-1.22	-5.36 to 3.11
		2004 - 2006	145-183	3152-3500	-15.99	-31.91 to 3.65
	4&5(Most Deprived)	1996 - 2000	142-209	3633-4991	-8.49*	-14.25 to -2.34
		2000 - 2004	145-200	3152-3500	1.24	-9.23 to 12.91
		2004 - 2006	145-179	3923-4501	-19.96	-37.21 to 2.00

APC: annual percent change *APC significantly different from 0%

Table 7-3 Joinpoint analysis of coronary heart disease mortality trends by age and deprivation in Scotland 1996-2006: Women aged over 35years

Age group [years]	Deprivation Category	periods	deaths, number (min-max)	Rates (min-max)	EAPC	95% CI for EAPC
35-54	1&2 (Most Affluent)	1996 - 2006	4-20	2-14	-6.54*	-9.76 to -3.20
	3	1996 - 2006	15-28	10-20	-5.66*	-9.11 to -2.07
	4 & 5 (Most Deprived)	1996 - 2006	25-57	17-42	-4.37*	-5.95 to -2.75
55-64	1&2 (Most Affluent)	1996 - 2006	14-60	21-117	-11.42*	-13.14 to -9.66
	3	1996 - 2006	43-84	64-147	-8.49*	-10.17 to -6.79
	4 & 5 (Most Deprived)	1996 - 2006	61-189	99-299	-6.22*	-7.92 to -4.47
65-74	1&2 (Most Affluent)	1996 - 2001	93-195	225-441	-7.52*	-9.98to -4.98
		2001 - 2006	59-136	133-294	-10.85*	-13.85 to -7.74
	3	1996 - 2006	142-312	275-604	-7.47*	-8.85 to -6.06
	4&5 (Most Deprived)	1996 - 1998	346-458	611-814	1.49	-3.80 to 7.07
		1998 - 2001	488-394	488-721	-7.97*	-13.16 to -2.46
		2001 - 2006	192-325	364-615	-3.59*	-5.01 to -2.13
75-84	1&2 (Most Affluent)	1996 - 2000	276-401	1045-1320	-4.18	-8.63 to 0.49
		2000 - 2006	221-368	719-1147	-7.74	-10.44 to -4.95
	3	1996 - 2006	314-527	867-1544	-5.66*	-6.73 to -4.56
	4&5 (Most Deprived)	1996 - 1998	581-665	1496-1819	-5.67	-11.03 to 0.01
		1998 - 2002	512-589	1301-1649	-2.88	-5.90 to 0.23
		2002 - 2006	342-488	1019-1357	-6.45*	-8.54 to -4.30
85+	1&2 (Most Affluent)	1996 - 2003	308-441	2548-3405	-2.48*	-4.18 to -0.75
		2003 - 2006	276-432	2588-3308	-7.62*	-14.02 to -0.74
	3	1996 - 2006	373-374	2267-3567	-2.55*	-3.68 to -1.40
	4&5(Most Deprived)	1996 - 2000	389-453	2906-3713	-4.70	-10.73 to 1.73
		2000 - 2004	331-453	2854-3308	1.31	-9.08 to 12.90
		2004 - 2006	321-391	2588-2738	-11.67	-30.21 to 1.79

APC: annual percent change *APC significantly different from 0%

Measuring deprivation is a complex task. Although the SIMD might not be an ideal measure of socio-economic position, it is probably at least as good a deprivation measure as the Carstairs or Townsend indices. [298,299] Because the SIMD health domain included an indicator of the Comparative Mortality Factor (CMF) for 2000-2004, caution was necessary when analyzing mortality data lest a tautology occur. However, our results were essentially unchanged when the analyses were repeated using only the income component of SIMD as the deprivation measure. Likewise, the SIMD 2006 may not accurately reflect deprivation during the entire period of our analysis.

A slowing of the rate of decline might simply reflect extremely low rates decreasing asymptotically as they approach zero. However, this would not explain the flattening in young men where rates were substantially higher than in women.

Has this phenomenon been seen elsewhere? Previous analyses of the flattening of mortality trends decline have mainly concentrated on age and sex effects in developed countries (England & Wales, USA and Australia). Surprisingly little attention has been paid to inequalities. Socio-environmental factors, particular the income component, have been associated with the time of onset of the decline phase of the coronary heart disease epidemic in the USA in the 60s-70s.[264] A comparison of mortality rates by educational level and occupational class in six European countries (Finland, Sweden, Norway, Denmark, England and Wales and Italy) showed that the decline in mortality among the socially disadvantaged was slower in the period 1983-1993.[300] In the US, the rate of heart disease and stroke mortality decline among the least educated was slower, particularly in African Americans with low educational levels.[301] In New Zealand, a cohort effect has been suggested with flattening of the observed decline in mortality and a predicted major increase in burden for Maoris and Pacific Islanders,(both relatively deprived compared to Europeans).[227]

Why might this mortality flattening remain confined to most deprived groups? A number of possible explanations for the social mortality gradients should be considered. Firstly, the distribution of major cardiovascular risk factors in the Scottish population showed marked socioeconomic gradients.[291] These “downstream” biological risk factors such as smoking, cholesterol and blood pressure will in turn be strongly patterned by “upstream” socio-economic factors such as low educational attainment, poor housing and inadequate income.

This also is consistent with the situation in Finland, where substantial decreases in cardiovascular mortality have been experienced in the last four decades, changes in risk factors are a stronger explanation for the mortality declines amongst the low socioeconomic groups as compared to the more affluent ones .[302]

Different levels and rates of change for cardiovascular risk factors in different socioeconomic groups may therefore make an important contribution to the continuing inequalities in coronary heart disease mortality. [292,303] In Scotland, the smoking rate in young adults is not declining as fast as in older groups. Furthermore, deprived groups continue to experience much higher smoking rates. [291] A recent study on Scottish coronary heart disease risk factor trends have looked at socioeconomic differentials in risk factors trends. [304] Although there were reduction is most adverse risk factors for coronary heart disease, the socioeconomic differentials have not been reduced over a decade. Even more, there was a hint of widening albeit not statistically significant, meaning that in deprived groups risk factors trends might have decline at a slower pace. More importantly, Hotchkiss et al found that self-reported diabetes and hypertension increased in prevalence over this period for all the socioeconomic groups. In the USA, although cholesterol and blood pressure improved in all socioeconomic groups, smoking and diabetes has actually increased amongst the more deprived.[305]

Much more probably, these mortality changes reflect social gradients in unhealthy behaviour, lifestyle and circumstances resulting in poor diet and high tobacco consumption leading to unfavourable levels of major coronary heart disease risk factors. These inequalities are persisting in spite of the widespread and constant health promotion and health prevention initiatives, which suggests substantial and continuing barriers to healthy changes. Increasing evidence suggests that younger and more deprived adults are less susceptible to preventative messages aimed at the general population. For example, it has been shown that lower income, less education and lower self efficacy all increase barriers to health promotion interventions.[303] Furthermore, marginalized minority and low-income groups may also receive less exposure to prevention messages on nutrition, exercise, and tobacco. [306] Although a role for decreased uptake of treatments among those most deprived groups cannot be discarded, this is probably modest, because the majority of premature coronary heart disease deaths occur outside hospital, half with no prior diagnosis of cardiovascular disease.[307,308]

Cocaine cardio- toxicity might play a role. However, the scale of its burden cannot explain totally this phenomenon, even taking into account the substantial underreporting. Although cocaine related deaths (all causes) have been increasing in the UK, the peak in 2004 was 184 (1022 since 1990). However only 36% of them were attributed to cocaine alone, and most happening in England & Wales.[309] Furthermore, cocaine related cardiac deaths often occur in the context of established atherosclerosis[310] and usually considered a triggering factor.[128]

Premature coronary heart disease deaths remain a potentially important contributor to social inequalities. Furthermore, the flattening mortality rates for coronary heart disease among younger adults may be the first warning signs of worsening lifestyle choices and behaviours rather than deterioration of medical management of coronary heart disease. Unfortunately, large time series of risk factor prevalence measures are not currently available for this population. This represents an important priority for future research, in order to estimate the extent to which trends in major cardiovascular risk factors may explain inequalities in coronary heart disease mortality. A better understanding the complex interaction of causal risk factors and inequalities will also be crucial.

Marked deterioration in medical management of coronary heart disease appears implausible. Thus, unfavourable trends in the major risk factors for coronary heart disease [smoking and poor diet], provide the most likely explanation for these apparent inequalities.

This is the first country where socioeconomic differentials in the pace of change of coronary heart disease mortality rates were described. The most plausible explanation is the net result of diverse dietary and risk factor trends, rather than deterioration of medical care.

In the next section, I will examine socio-economic differentials in coronary heart disease mortality rates in England, to explore whether the observed mortality flattening shows any evidence of socio-economic patterning similar to that in Scotland.

7.3 CORONARY HEART DISEASE MORTALITY TRENDS IN ENGLAND BY SOCIOECONOMIC CIRCUMSTANCES, 1982-2006

7.3.1 Introduction

England is an interesting setting for further exploring the relationship of socioeconomic level and coronary heart disease mortality trends, particularly because of the quality and similarity of the data to that available in Scotland. Thus, a comparison of the two countries might shed further insights regarding the drivers of the speed of change of these mortality trends.

Recent flattening in mortality rates trends has been described both in Scotland and in England and Wales. In Scotland, the flattening is happening essentially amongst young deprived adults. There are no reports of age-specific socioeconomic trend differentials in England and Wales, although important socioeconomic differentials in mortality rates and risk factors has been described.[6,106]

Our aim was therefore to analyze recent age, gender and socioeconomic specific coronary heart disease mortality trends in England during the period 1982-2006.

7.3.2 Methods

Data

We used the Index of Multiple Deprivation 2007 (IMD) as our indicator of socioeconomic circumstances.[311] The IMD is a measure of multiple deprivation at the small area level, the Lower Layer Super Output Area (LSOA), an area covering an average of 1,500 people. The overall IMD score is a weighted composite of indicators measuring seven domains of deprivation (income; employment; health and disability; education, skills and training; barriers to housing and services; crime; living environment). We grouped LSOAs into equal fifths of areas ranked by increasing IMD score. This IMD score remained fixed over the period of analysis Corresponding LSOA mid-year population estimates by five year age-group and sex for the period 2001-07 were provided by ONS (as 'experimental statistics')[312]. For 1981-2000, we estimated populations by extending previous work using a cohort-component model with outputs constrained to sum to the ONS sub national estimates for each year.[313] All age-sex estimates were aggregated into the deprivation quintiles described above.

We obtained mortality data by year of registration of death for the period 1981 to 2007 from the Office for National Statistics (ONS). For each year, ONS provided counts of deaths aggregated up to 3-digit International Classification of Diseases (ICD) codes in five year age bands by sex for each of our five deprivation groups. We determined underlying cause of death from coronary heart disease by selecting on ICD-9 (ninth revision) codes 410-414 for the period 1981-2000 and ICD-10 (tenth revision) codes I20-I25 for 2001-07. We limited our analyses to people aged 35 years and older. Rates were standardised using the European standard as the reference population. To reduce the year on year variability in age-specific rates, we calculated rates for 10 year age bands (to age 85 and over) using three year moving averages. We quote just the central year to denote each three-year interval.

Statistical analysis

We used age-adjusted rate difference and rate ratio between the least and most deprived areas to quantify absolute and relative inequality. We used Joinpoint Regression Programme (version 3.4.2, Oct 2009) to estimate periods with similar annual percentage change in mortality rates. We used a Bayesian information criterion approach and allowed a maximum of three joinpoints (i.e. four segments). In addition to the annual percentage change (APC) over each segment, Joinpoint also calculates a weighted average annual percentage change (AAPC) over the whole 25 years of the study.

7.3.3 Results

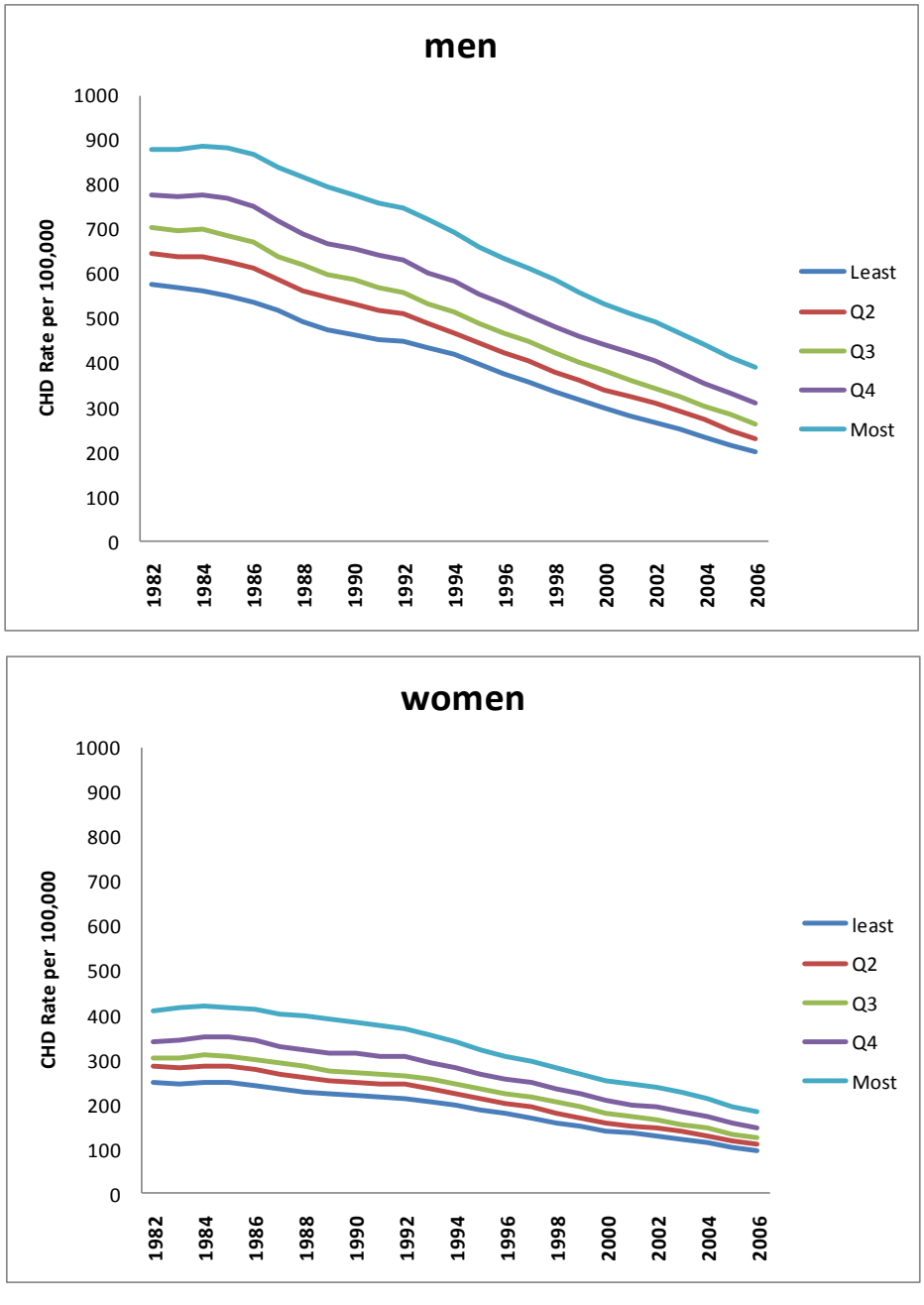
Overall change in age-adjusted CHD mortality rates

Between 1982 and 2006, the age standardised rate for CHD mortality in England fell by 62.2% in men and 59.7% in women (see appendix A31A3) . Rates declined slightly faster for men than for women (averaging 4.0% and 3.7% per year, respectively). However, absolute rates remained more than twice as high for men compared to women throughout the period. CHD mortality rates in men reached a similar level in 2006 (272 per 100,000) as those in women more than a decade previously (280 per 100,000 in 1992)

The rapid decline in CHD mortality was observed in all deprivation groups. Thus, the absolute gap in age-adjusted death rates between the most and least deprived groups fell by two-thirds for men (from 300 per 100,000 in 1982 to 190 per 100,000 in 2006) and almost halved for women (from 161 to 87 per 100,000, respectively) (Figure 7-7). However, the narrowing of the absolute inequality

gap was accompanied by a significant widening in the rate ratio between deprived and affluent groups because rates fell more slowly for men and women living in the most deprived areas (3.3% per year for both) compared with the fall in rates observed in the most affluent areas (men 4.3% and women 3.9% per year) (Figure 7-8). Even the differential pace of decline, the rate ratio for men therefore rose from 1.52 (95% CI: 1.50-1.54) to 1.94 (95% CI: 1.90-1.97); and for women, from 1.64 (95%CI: 1.62-1.67) to 1.90 (95% CI: 1.86-1.94). Thus, over the quarter century, absolute inequality in CHD mortality has declined but relative inequality has increased.

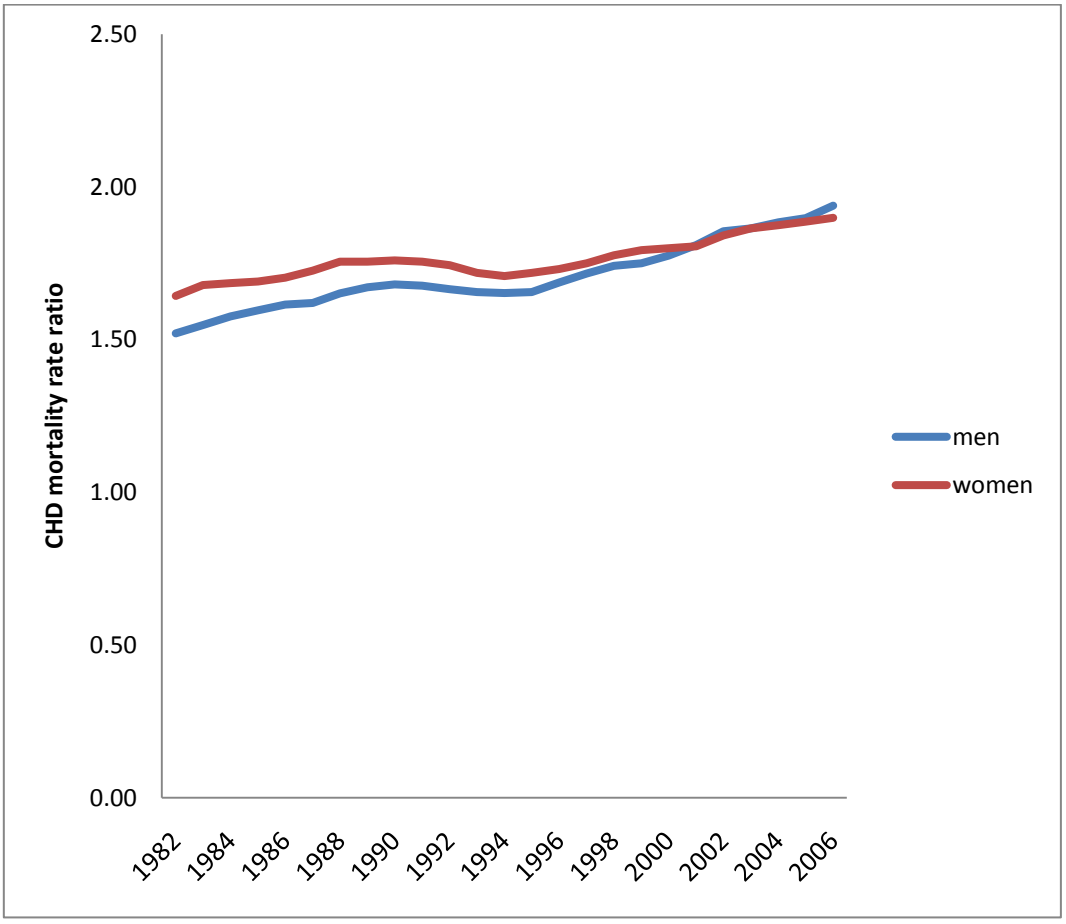
Figure 7-7 Age standardized CHD mortality rates by IMD, England 1982-2006



CHD mortality rates fell for all age groups and across all deprivation quintiles between 1982 and 2006. Absolute inequalities therefore narrowed in each age and sex group (Figure 7-9). However, relative inequalities widened over the same period because death rates fell differentially.

In 2006 there was a four-fold difference in rate ratios for men and a six-fold difference for women aged 35-44 (Figure 7-10 and 7-11). The rate ratio was largest for the youngest age groups and became successively shallower for older ages until by age 85 and over it stood at just a little over one, signifying only a small mortality disadvantage in the most deprived groups relative to the most affluent. Not only were the CHD mortality rate ratios larger in younger ages, they also widened more over time (Figure 7-12). This was more clearly visible for men because rates for young women were particularly low in the least deprived areas (under 10 per 100,000 women from 1990 onwards in the age groups 35-44 and 45-54), and therefore subject to erratic fluctuations from one year to the next. Rate ratios drifted upwards over time because of the social gradient in the pace of decline in age-specific rates. Rates fell further in the more advantaged areas than in the deprived areas.

Figure 7-8 CHD mortality rate ratios between most and least deprived groups, by gender. England, 1982-2006.



The social gradient in the Average Annual Rates of Fall (or AAPCs) was most marked between ages 55-64 to 75-84 where the majority of CHD deaths occur. Among those aged 85 and over, rates of fall were modest (about 2% per annum) and the pace of fall did not vary significantly between deprivation quintiles (Figure 7-9). As a result, the rate ratios for those aged 85 and over stood at just over 1 throughout the whole period despite rate difference in this age narrowing by about a fifth (Figure 7-12).

The average annual rate of fall over the period was larger for men than women aged up to 54, but was higher for women than men aged 55 to 84 converging finally at age 85 and over (Figure 7-9).

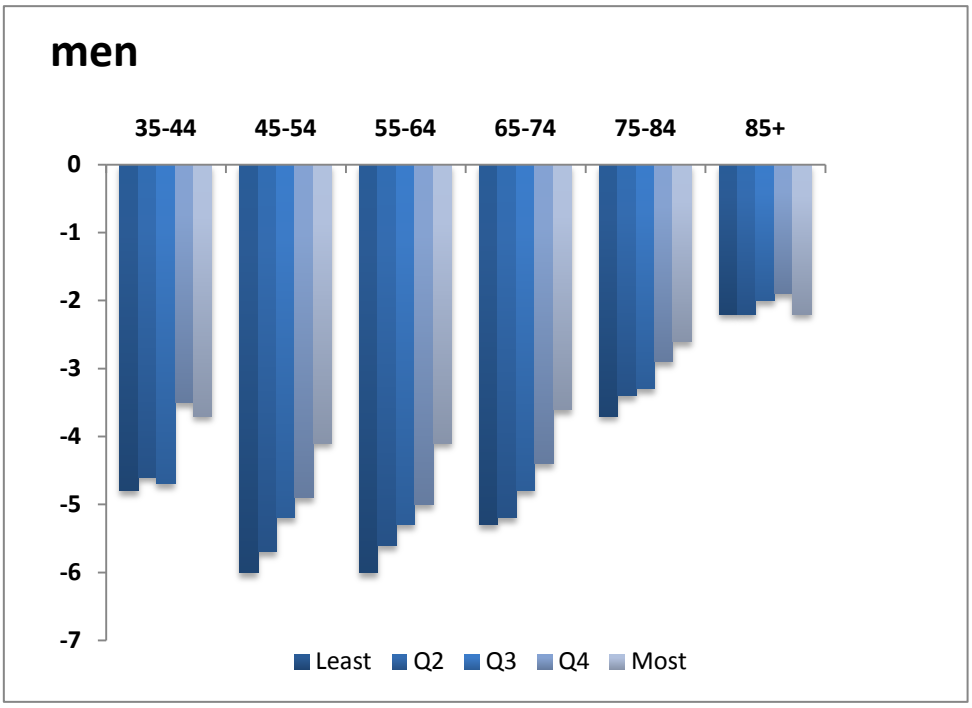
Time trend analysis - overall, by age, sex and deprivation quintile

The annual rate of decline in CHD mortality in men for England was steeper in the most recent period from about 2000 onwards for most age bands above 45 years. (Table 7-4) The exact year when the rate of decline accelerated varied across different ages. In contrast, for ages 35-44, the overall rate of decline for England slowed significantly from -4.7% per year (-4.6% to -3.3%) in 1994-2000 to -2.9% per year (-2.0% to -3.9%) in 2000-2006.

The average annual percentage decline in rates for women exhibited a similar magnitude and pattern of accelerated falls in the most recent period in the older age groups (Table 7-5). Rates for the youngest age band (35-44) were very unstable with no clear pattern detectable in the most recent period (reflecting small numbers of events). In the next higher age band (age 45-54) the overall pace of fall doubled in the most recent segment (from - 2.7% (-2.2% to -3.2%) in 1995-2002 to -6.2%, (-5.2% to -7.2%) in 2002-2006.

In men , a similar flattening in the rate of fall in younger adults was seen in all quintiles except the third quintile.(Table 7-5) In women, however, the APCs for the two most affluent quintiles flattened substantially (to 1.0% in quintile 1, not significantly different from 0% at the 95% confidence level) and actually reversed for quintile two with rates rising by about 5% per year between 2003-2006 (+4.9%, 1.0% to 8.9%) (Table 7-6)

Figure 7-9 Average annual percentage change (AAPC) in CHD mortality rates by age and deprivation, England 1982-2006



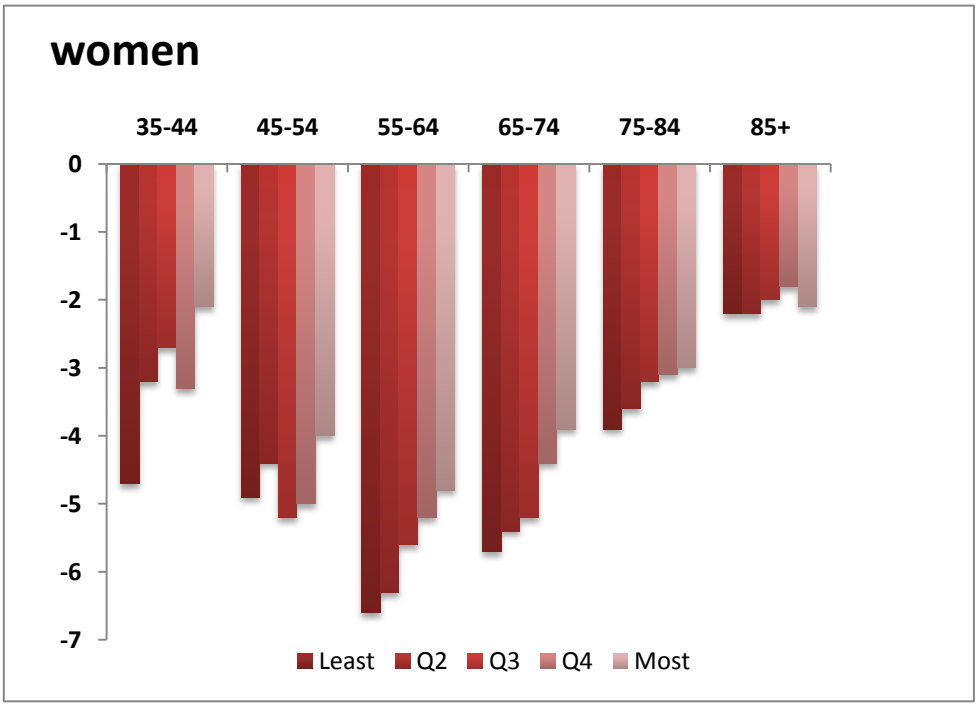


Figure 7-10 CHD mortality trends by age and deprivation, men, England 1982-2006

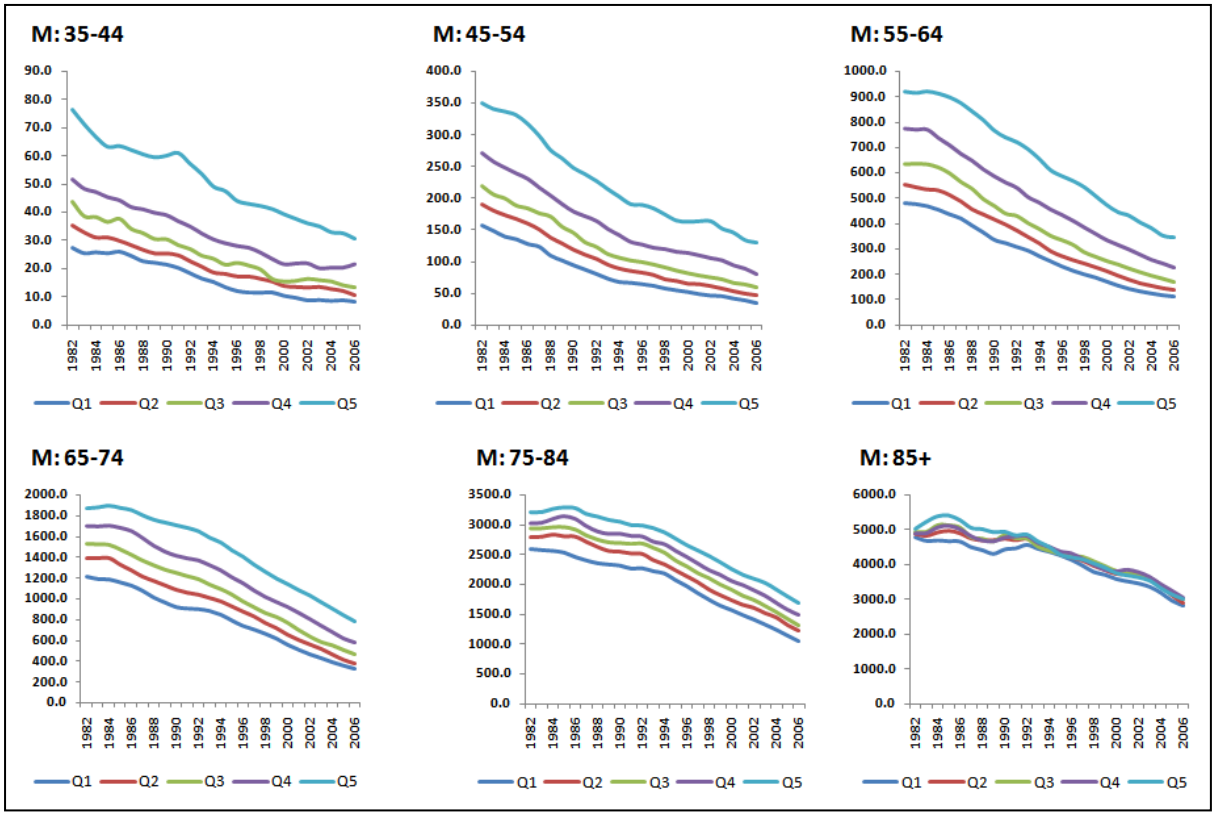


Figure 7-11 CHD mortality trends by age and deprivation, women, England 1982-2006.

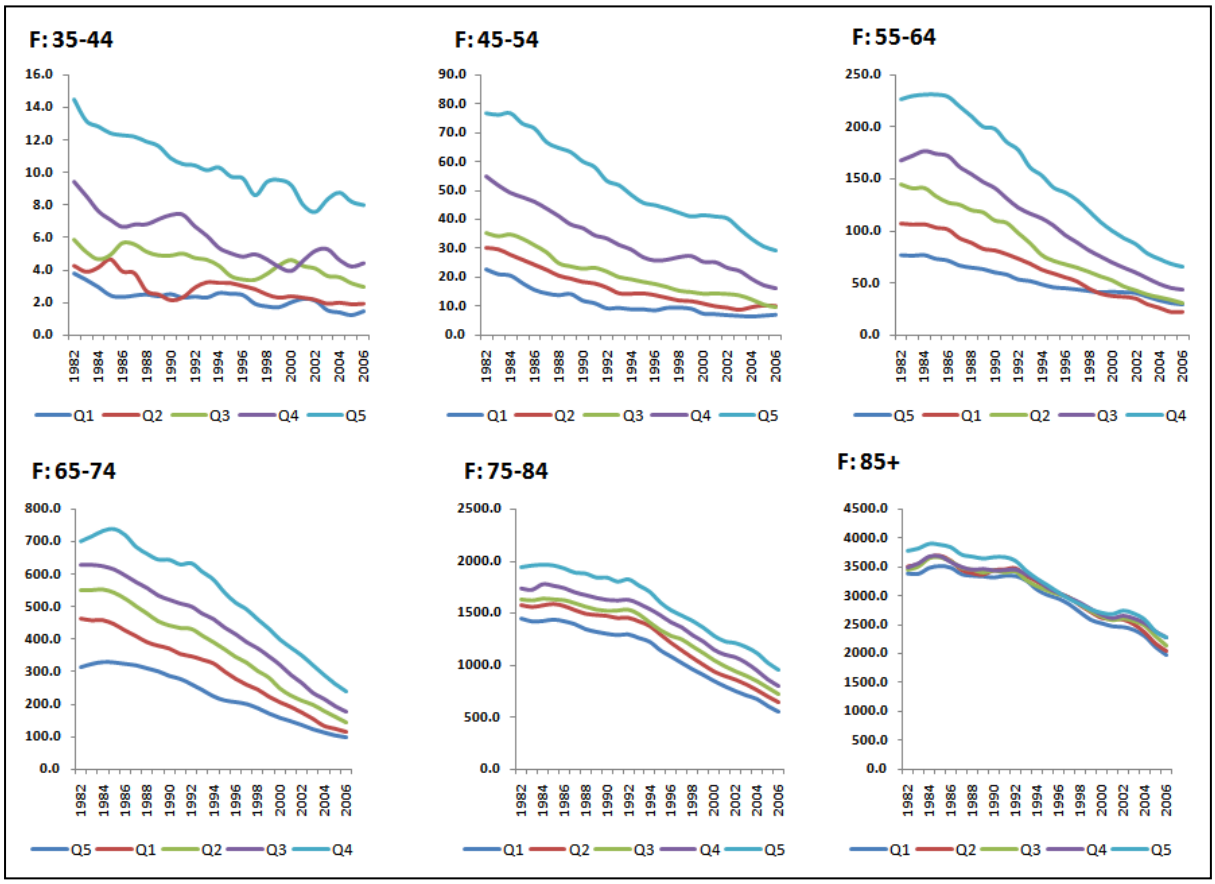


Figure 7-12 Trends in CHD mortality rate ratios between most and least deprived groups by age group, England 1982-2006

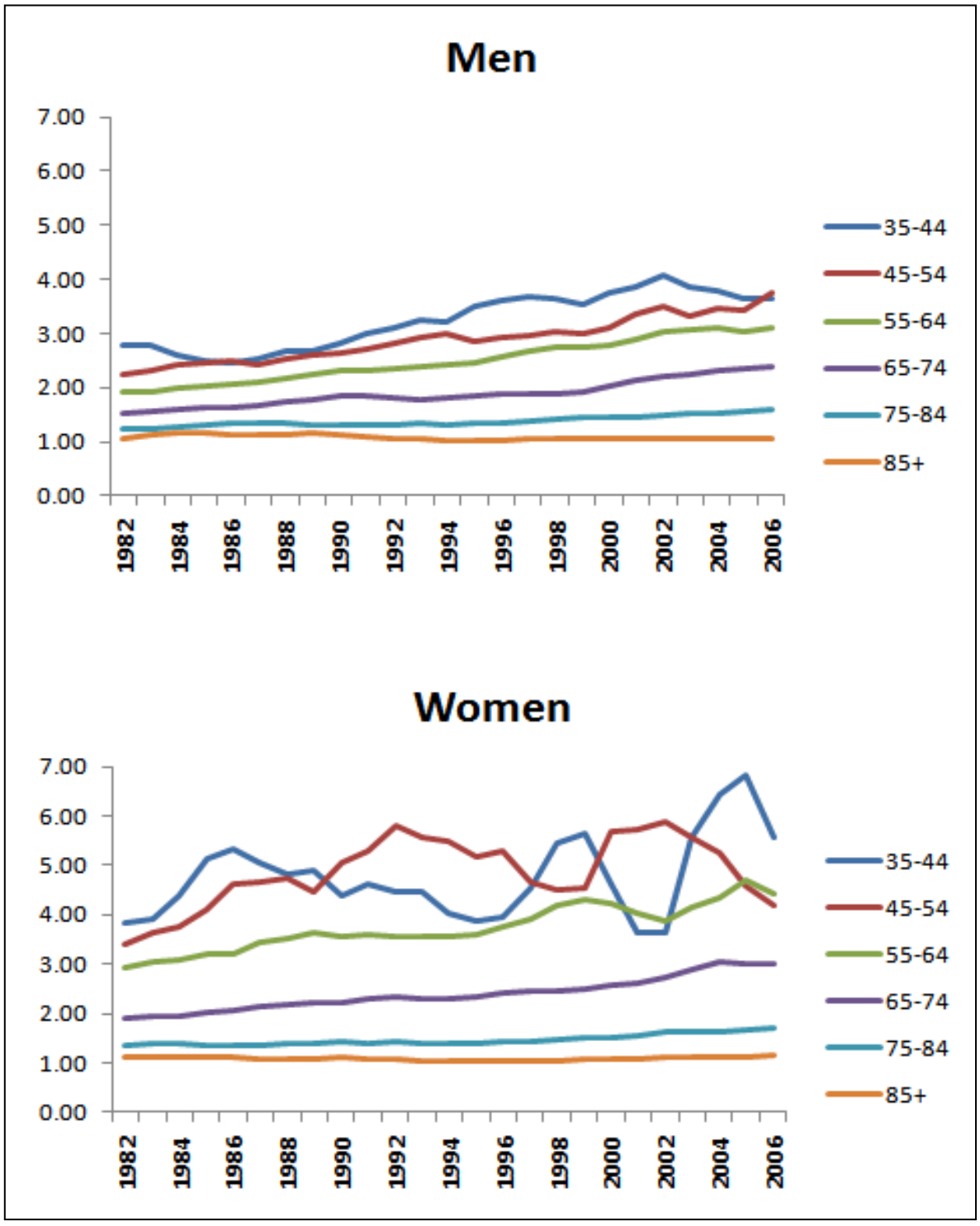


Table 7-4 CHD mortality trends by age and deprivation, men, England 1982-2006

Age	England		By deprivation quintile									
			Q1 (least deprived)		Q2		Q3		Q4		Q5 (most deprived)	
	year	APC (95% CI)	year	APC (95% CI)	year	APC (95% CI)	year	APC (95% CI)	year	APC (95% CI)	year	APC (95% CI)
35-44	82-91	-3.4* (-3.7 to -3)	82-86	-1.1 (-3.6 to 1.4)	82-91	-3.9* (-4.5 to -3.2)	82-97	-4.7* (-5.1 to -4.2)	82-90	-3.3* (-3.8 to -2.8)	82-85	-6.2* (-7.7 to -4.6)
	91-94	-6.5* (-1.7 to -11)	86-91	-4.4* (-6.8 to -1.9)	91-94	-7.9 (-15.6 to 0.5)	97-00	-9.6 (-20.9 to 3.3)	90-00	-5.2* (-5.7 to -4.7)	85-91	-0.8 (-1.5 to 0.0)
	94-00	-4.7* (-3.6 to -5.9)	91-96	-9.5* (-12.3 to -6.6)	94-06	-4.3* (-4.9 to -3.7)	00-03	1.9 (-11.1 to 16.8)	00-04	-2.7 (-5.7 to 0.4)	91-95	-6.0* (-7.8 to -4.2)
	00-06	-2.9* (-2 to -3.9)	96-06	-4.0* (-4.9 to -3.1)			03-06	-6.4 (-12.8 to 0.5)	04-06	3.1 (-3.0 to 9.6)	95-06	-3.7* (-4.0 to -3.4)
45-54	82-86	-3.7* (-3.1 to -4.4)	82-87	-4.9* (-5.6 to -4.2)	82-86	-4.1* (-5.0 to -3.2)	82-88	-4.0* (-4.5 to -3.5)	82-86	-3.9* (-4.7 to -3.1)	82-85	-1.8 (-3.9 to 0.4)
	86-94	-6.7* (-6.4 to -7)	87-93	-8.0* (-8.8 to -7.2)	86-94	-7.1* (-7.5 to -6.6)	88-93	-7.8* (-8.8 to -6.8)	86-96	-5.8* (-6.1 to -5.5)	85-95	-5.3* (-5.8 to -4.9)
	94-03	-3.8* (-3.5 to -4.1)	93-03	-4.7* (-5.1 to -4.3)	94-02	-4.7* (-5.2 to -4.2)	93-03	-4.3* (-4.6 to -4.0)	96-03	-2.9* (-3.5 to -2.2)	95-03	-2.7* (-3.5 to -1.9)
	03-06	-6.1* (-4.6 to -7.6)	03-06	-7.9* (-10.4 to -5.2)	02-06	-6.4* (-7.8 to -5.0)	03-06	-6.0* (-8.1 to -3.8)	03-06	-7.7* (-9.7 to -5.7)	03-06	-5.7* (-8.8 to -2.4)
55-64	82-85	-0.8 (0 to -1.6)	82-85	-1.4 (-3.0 to 0.2)	82-85	-1.1 (-2.5 to 0.3)	82-85	-0.5 (-1.6 to 0.7)	82-84	-0.1 (-1.0 to 0.9)	82-86	-0.4 (-1.1 to 0.3)
	85-93	-4.9* (-4.6 to -5.1)	85-94	-5.7* (-6.1 to -5.3)	85-91	-4.8* (-5.4 to -4.1)	85-94	-5.4* (-5.7 to -5.2)	84-92	-4.4* (-4.6 to -4.3)	86-93	-3.9* (-4.3 to -3.5)
	93-06	-6.5* (-6.4 to -6.6)	94-04	-7.6* (-8.0 to -7.2)	91-06	-6.8* (-7.0 to -6.7)	94-06	-6.4* (-6.6 to -6.2)	92-97	-5.2* (-5.6 to -4.8)	93-98	-4.8* (-5.8 to -3.9)
			04-06	-4.7 (-9.9 to 0.7)					97-06	-6.4* (-6.5 to -6.2)	98-06	-5.6* (-6.0 to -5.2)

Table 7-4 (continued)

Age	England		By deprivation quintile									
			Q1 (least deprived)		Q2		Q3		Q4		Q5 (most deprived)	
	year	APC (95% CI)	year	APC (95% CI)	year	APC (95% CI)	year	APC (95% CI)	year	APC (95% CI)	year	APC (95% CI)
65-74	82-84	0.0 (1.9 to -2)	82-84	-1.1 (-5.9 to 3.9)	82-84	-0.9 (-3.6 to 1.8)	82-84	-0.5 (-2.5 to 1.6)	82-85	-0.5 (-1.9 to 1.0)	82-84	1.0 (-0.1 to 2.1)
	84-94	-3.0* (-2.8 to -3.1)	84-94	-3.5* (-3.9 to -3.0)	84-96	-3.5* (-3.7 to -3.3)	84-94	-3.1* (-3.3 to -2.9)	85-94	-3.0* (-3.4 to -2.7)	84-93	-1.8* (-1.9 to -1.7)
	94-00	-5.7* (-5.2 to -6.2)	94-98	-5.4* (-8.1 to -2.6)	96-03	-7.4* (-7.9 to -6.8)	94-99	-5.6* (-6.4 to -4.9)	94-01	-5.2* (-5.8 to -4.6)	93-02	-4.8* (-5.0 to -4.7)
	00-06	-7.8* (-7.4 to -8.3)	98-06	-8.5* (-9.2 to -7.8)	03-06	-10.1* (-12.1 to -8.1)	99-06	-7.7* (-8.0 to -7.3)	01-06	-7.8* (-8.8 to -6.8)	00-06	-6.7* (-7.2 to -6.1)
75-84	82-85	0.2 (1.3 to -1)	82-94	-1.5* (-1.6 to -1.3)	82-84	1.1 (-2.1 to 4.4)	82-84	0.7 (-2.6 to 4.0)	82-85	0.9 (-0.7 to 2.5)	82-85	0.9* (0.0 to 1.9)
	85-94	-1.7* (-1.5 to -1.9)	94-03	-5.3* (-5.5 to -5.0)	84-93	-1.7* (-2.0 to -1.4)	84-94	-1.5* (-1.8 to -1.3)	85-94	-1.7* (-2.0 to -1.3)	85-94	-1.5* (-1.7 to -1.3)
	94-2003	-4.6* (-4.3 to -4.9)	03-06	-7.4* (-8.6 to -6.1)	93-04	-4.6* (-4.9 to -4.4)	94-2003	-4.7* (-5.1 to -4.4)	94-03	-4.2* (-4.5 to -3.8)	94-2003	-3.9* (-4.1 to -3.7)
	03-06	-6.9* (-5.6 to -8.2)			04-06	-8.2* (-11.6 to -4.7)	03-06	-7.3* (-9.1 to -5.4)	03-06	-6.5* (-8.3 to -4.7)	03-06	-5.7* (-6.8 to -4.6)
85+	82-92	-0.7* (-0.3 to -1.1)	82-89	-1.4* (-2.0 to -0.9)	82-92	-0.4* (-0.7 to -0.1)	82-84	1.7 (-4.3 to 8.0)	82-92	-0.5 (-0.9 to 0.0)	82-84	3.6 (-0.4 to 7.8)
	92-2003	-2.5* (-2.2 to -2.8)	89-92	1.7 (-1.9 to 5.4)	92-00	-2.8* (-3.2 to -2.4)	84-92	-1.1* (-1.8 to -0.4)	92-99	-2.9* (-3.8 to -2.0)	84-92	-1.6* (-2.1 to -1.1)
	03-06	-5.7* (-3.7 to -7.7)	92-03	-2.9* (-3.1 to -2.6)	00-06	-0.9 (-3.8 to 2.2)	92-03	-2.3* (-2.7 to -1.9)	99-02	-0.7 (-5.8 to 4.7)	92-03	-2.8* (-3.0 to -2.5)
			03-06	-5.5* (-7.0 to -4.0)	03-06	-7.5* (-8.9 to -6.1)	03-06	-5.7* (-7.9 to -3.3)	03-06	-5.3* (-6.9 to -3.7)	03-06	-5.1* (-6.7 to -3.4)

Notes: * Trend significantly different from 0

Table 7-5 CHD mortality trends by age and deprivation, women, England 1982-2006

Age	England		By deprivation quintile									
			Q1 (least deprived)		Q2		Q3		Q4		Q5 (most deprived)	
	year	APC (95% CI)	year	APC (95% CI)	year	APC (95% CI)	year	APC (95% CI)	year	APC (95% CI)	year	APC (95% CI)
35-44	82-84	-7.9* (-1.7 to -13)	82-85	-12.7 (-24.2 to 0.4)	82-85	4.7 (-2.9 to 13.0)	82-93	-1.2* (-2.4 to 0.0)	82-86	-8.4* (-13.9 to -2.6)	82-02	-2.5* (-2.8 to -2.2)
	84-06	-2.4* (-2.2 to -2.5)	85-01	-1.4* (-2.7 to 0.0)	85-90	-14.0* (-18.5 to -9.4)	93-96	-12.0 (-27.9 to 7.3)	86-91	2.7 (-3.7 to 9.5)	02-06	0.2 (-3.5 to 3.9)
			01-06	-9.4* (-16.3 to -1.9)	90-93	15.7 (-3.6 to 38.9)	96-00	9.1 (-1.0 to 20.4)	91-95	-10.4 (-19.7 to 0.1)		
					93-06	-4.5* (-5.4 to -3.6)	00-06	-7.0* (-10.0 to -3.9)	95-06	-0.6 (-2.1 to 1.0)		
45-54	82-84	-2.8* (-0.5 to -5)	82-94	-7.9* (-8.7 to -7.1)	82-93	-6.3* (-6.7 to -5.9)	82-85	-1.1 (-5.0 to 2.9)	82-96	-5.2* (-5.4 to -4.9)	82-84	0.6 (-3.5 to 5.0)
	84-95	-5.8* (-5.6 to -6)	94-98	2.6 (-5.5 to 11.3)	93-96	-2.9 (-8.9 to 3.5)	85-88	-9.2* (-16.8 to -0.9)	96-99	1.0 (-5.5 to 7.9)	84-97	-4.4* (-4.7 to -4.1)
	95-02	-2.7* (-2.2 to -3.2)	98-02	-8.7* (-16.2 to -0.6)	96-03	-5.7* (-6.9 to -4.6)	88-04	-4.3* (-4.8 to -3.9)	99-03	-5.1* (-8.3 to -1.8)	97-02	-1.5 (-3.2 to 0.3)
	02-06	-6.2* (-5.2 to -7.2)	02-06	1.0 (-4.9 to 7.2)	03-06	4.9* (1.0 to 8.9)	04-06	-12.1 (-22.9 to 0.1)	03-Jun	-10.5* (-14.0 to -6.9)	02-06	-8.0* (-9.8 to -6.2)
55-64	82-85	0.4 (1.6 to -0.8)	82-85	-1.0 (-4.2 to 2.3)	82-91	-3.3* (-3.7 to -3.0)	82-84	3.1* (0.5 to 5.8)	82-85	1.0 (-0.5 to 2.5)	82-85	1.6 (-0.2 to 3.4)
	85-90	-3.8* (-3 to -4.6)	85-93	-5.0* (-6.0 to -4.1)	91-95	-10.1* (-12.4 to -7.8)	84-87	-2.7* (-5.1 to -0.1)	85-90	-3.4* (-4.3 to -2.4)	85-89	-2.2* (-4.0 to -0.4)
	90-98	-6.6* (-6.2 to -7)	93-02	-7.8* (-8.8 to -6.9)	95-98	-4.7 (-9.9 to 0.9)	87-95	-5.5* (-5.8 to -5.1)	90-97	-6.0* (-6.6 to -5.4)	89-98	-5.3* (-5.8 to -4.8)
	98-06	-8.4* (-8 to -8.9)	02-06	-10.7* (-13.9 to -7.4)	98-06	-8.4* (-9.0 to -7.7)	95-06	-7.9* (-8.1 to -7.6)	97-06	-7.5* (-7.9 to -7.1)	98-06	-7.8* (-8.4 to -7.2)

Table 7-5 (continued)

Age	England		By deprivation quintile									
			Q1 (least deprived)		Q2		Q3		Q4		Q5 (most deprived)	
	year	APC (95% CI)	year	APC (95% CI)	year	APC (95% CI)	year	APC (95% CI)	year	APC (95% CI)	year	APC (95% CI)
65-74	82-85	-0.1 (1 to -1.1)	82-84	-0.7 (-3.9 to 2.6)	82-84	0.5 (-3.8 to 4.9)	82-84	0.1 (-1.6 to 1.9)	82-84	2.9 (-1.5 to 7.4)	82-85	0.8 (0.0 to 1.5)
	85-94	-2.8* (-2.6 to -3.1)	84-94	-3.4* (-3.7 to -3.1)	84-94	-3.4* (-3.8 to -3.0)	84-94	-3.0* (-3.2 to -2.8)	84-94	-2.3* (-2.7 to -1.9)	85-93	-1.6* (-1.8 to -1.4)
	94-00	-6.3* (-5.8 to -6.9)	94-01	-7.2* (-7.8 to -6.5)	94-98	-6.2* (-8.7 to -3.6)	94-99	-5.4* (-6.1 to -4.7)	94-02	-6.2* (-6.9 to -5.5)	93-03	-5.5* (-5.7 to -5.3)
	00-06	-8.8* (-8.3 to -9.4)	01-06	-10.3* (-11.5 to -9.2)	98-06	-8.8* (-9.5 to -8.0)	99-06	-9.3* (-9.7 to -9.0)	02-06	-9.3* (-11.5 to -7.1)	03-06	-8.7* (-9.9 to -7.4)
75-84	82-84	0.5 (2.9 to -1.9)	82-85	-0.1 (-1.4 to 1.3)	82-85	0.0 (-1.5 to 1.5)	82-85	0.0 (-1.7 to 1.7)	82-84	1.4 (-1.4 to 4.2)	82-84	0.8 (-2.2 to 3.9)
	84-93	-1.2* (-0.9 to -1.4)	85-94	-1.7* (-2.0 to -1.4)	85-93	-1.2* (-1.5 to -0.8)	85-93	-1.1* (-1.5 to -0.6)	84-94	-1.3* (-1.5 to -1.1)	84-93	-1.3* (-1.6 to -0.9)
	93-04	-5* (-4.8 to -5.2)	94-04	-5.8* (-6.1 to -5.6)	93-04	-5.6* (-5.9 to -5.4)	93-03	-4.9* (-5.2 to -4.5)	94-03	-4.6* (-4.9 to -4.3)	93-04	-4.2* (-4.5 to -3.9)
	04-06	-8.7* (-5.5 to -11.7)	04-06	-8.8* (-12.0 to -5.4)	04-06	-8.0* (-11.8 to -4.1)	03-06	-7.0* (-9.2 to -4.8)	03-06	-7.5* (-9.3 to -5.7)	04-06	-7.0* (-11.2 to -2.6)
85+	82-92	-0.5* (-0.2 to -0.9)	82-92	-0.3 (-0.7 to 0.1)	82-92	-0.5* (-1.0 to 0.0)	82-84	3.0 (-2.2 to 8.5)	82-93	-0.6* (-0.9 to -0.3)	82-92	-0.8* (-1.1 to -0.4)
	92-00	-3.3* (-2.7 to -3.9)	92-00	-3.4* (-4.0 to -2.9)	92-04	-3.0* (-3.4 to -2.6)	84-92	-1.0* (-1.7 to -0.4)	93-00	-3.4* (-4.2 to -2.6)	92-99	-3.9* (-4.5 to -3.2)
	00-03	-0.8 (4 to -5.4)	00-03	-1.4 (-5.5 to 2.9)	04-06	-7.5* (-13.4 to -1.3)	92-04	-2.6* (-2.9 to -2.3)	00-03	-0.6 (-5.4 to 4.5)	99-03	-0.2 (-2.3 to 2.0)
	03-06	-5.9* (-3.5 to -8.2)	03-06	-6.4* (-8.5 to -4.3)			04-06	-6.4* (-10.9 to -1.7)	03-06	-4.6* (-7.0 to -2.1)	03-06	-5.6* (-7.8 to -3.4)

Notes: APC: annual percent change * Trend significantly different from 0

7.3.4 Interpretation

Substantial social inequalities in CHD mortality persisted in England throughout the period 1982-2006. This was despite dramatic falls in the incidence rates of CHD deaths. Age-adjusted CHD death rates rose progressively with increasing area deprivation for both sexes. However, the rate difference (gap between the most and least deprived quintiles) closed year on year such that by 2006 absolute inequalities were approximately half those in 1982. However, because the pace of fall was steeper in the more affluent areas, relative inequalities widened over the same period.

The pattern was repeated consistently in both sexes and for all ages except in the oldest – thus, that over time absolute differences declined while relative inequalities increased. Relative inequalities were largest at younger ages with the gradient becoming progressively shallower and disappeared above age 85. The larger the social gradient at the baseline, the more it widened over time. Thus, the youngest age groups for which the social gradients were already the largest in 1982 became progressively wider over the 25 years of this study.

This study adds more information to my previous reporting of the flattening observable in England & Wales. First, the flattening is still evident in the younger age groups after updating the time series, crucially by adding a few years at the end. This is particularly noticeable for men and women aged 45-54. In my previous analysis, these groups experienced a slowing down in the two last periods, starting in 1993.In this updated analysis the flattening is confirmed for the period 1993-2003 (1993-2002 for women), but accelerated afterwards, a pattern that resembles the observed in the Netherlands. A recent analysis of the WHO health for all database, focusing in adults aged-standardized rates for adults aged 35-44 , didn't found this flattening in England & Wales, but confirmed the flattening periods in Scotland and the "speed up" observed in the Netherlands.[314] They looked at a similar time period as we did in this updated analysis, but instead defined "fixed periods" 1985-89 to 1995-99 and then for 95-99 to 2005-07, and calculated relatives declines. The results for England & Wales in that study showed that the average annual percent change in those periods decreased from 38.5% to 28.5%, suggesting nonetheless a slowing down of the rate in young adults. These findings highlights the need for constantly update the trend analysis using change-point methods, as new information is available.

Interestingly, absolute differentials are observed across most quintiles. These strengthen the idea that the slowing down in CHD mortality rates is a real phenomenon, and not an artefact attributable to low or unstable rates.

In the Scottish analysis we hypothesized that socioeconomic differentials in the rate of decline by age can be explained by socioeconomic differentials in risk factors. The English data showed some differences in the rate of decline by socioeconomic status. For example, women aged 45-54 in the most affluent quintiles showed slower pace of decline compared to the most deprived quintiles, tough the general picture is that there is not a clear-cut pattern as the one described in Scotland.

In other setting, socioeconomic differentials in the pace change have been observed, but without looking at age specific rates. Marked social differences, with widening of the inequality gap in coronary heart disease mortality rates has been described in six European countries.[300] In the US, slower decline in CHD and stroke in the least educated was observed, particularly in African Americans with low educational attainment.[301] And in New Zealand Maoris and Pacific Islanders, considered more deprived than Europeans, slowing of their CHD mortality rate of decline has been described.[227]

Why there are no clear socioeconomic patterns in the pace of decline observed in England? Preliminary evidence on risk factor in England showed that trends by socioeconomic status are complex. Between 1994 and 2008, the prevalence of smoking, high blood pressure and raised cholesterol decreased in most deprivation quintiles. However, there are increasing inequalities in obesity, diabetes and cholesterol levels in older people, and high blood pressure in younger women.[315] The net effect of these diverse trends on rates is therefore difficult to estimate, and might explain the lack of socioeconomics gradients in the trend pattern.

This study is based on a larger population; therefore, the rates are more robust. This suggests that the lack of a clear socio-economic gradient in the pace of change is not due to lack of power.

This study has limitations. Misclassification of cause of death in young adults and the elderly over time and by deprivation area is possible, although unlikely given the high quality of mortality registration in England, as in Scotland. Misclassification of socioeconomic level at the time of death is also possible, as we use only just one measure of socioeconomic level for the entire trend. This could also bias the comparison between the two countries if the misclassification rate in both counties differs systematically.

Substantial methodological difficulties might still hamper the comparison of socioeconomic mortality differentials between populations when using area-based measures of socio-economic position. For example, differential rates of concentration of more deprived areas (*"polarization by selective migration or increasing pauperizations"*)[316] might result in areas at the same quintile deprivation level but with substantial differences in health. This might also operate within a geographically defined population, as people with poorer health move differentially across areas within the geographical boundaries. Furthermore, uncertainties in the way small area population structure estimation (needed to calculate deprivation and mortality rates by deprivations status) might bias the findings and the comparison between the two countries.

The inclusion of the health and disability component of the SIM to analyze mortality rate might induced some circular inference, creating a dependence of the socio-economic classification on the health outcome we are analyzing. Reassuringly, removing these components tends not to alter the results of other analyses.

An intriguing possibility is yet unexplained mortality differences between Scotland and England, the so called "Scottish Effect".[317] However, the higher mortality in Scotland is increasingly unexplained by socioeconomic factors[317], even using approaches that take into account the life course socioeconomic position.[318] One of the explanations offered is that Scots have higher levels of risk factors compared with their English counterparts at the same deprivation level. This might result in a different absolute risk for the same deprivation level and therefore a different trend. Furthermore, the deprived Scottish population might be at a slightly different phase of the epidemic compared to equally deprived people in England.

In conclusion, overall trends represent the net result of diverse underlying treatment and risk factor trends, some favourable and some unfavourable, operating in the population over a defined period. I have discussed earlier that the observed recent trend patterns in many countries are probably related more to changes in risk factors than to changes in treatments. Poland offered an informative case study in Chapter 6. Because risk factors frequently demonstrate strong socioeconomic gradients in the UK, their contribution to these trends might also vary by socioeconomic status. However, no studies quantifying the contribution of risk factors and treatments by socio-economic status have yet been conducted in the UK.

In the next section I will therefore describe the first study to explore this issue in detail.

7.4 ANALYSING RECENT SOCIOECONOMIC TRENDS IN CORONARY HEART DISEASE MORTALITY IN ENGLAND, 2000-2007: A POPULATION MODELLING STUDY

7.4.1 Introduction

Since the 1970s, coronary heart disease (CHD) mortality in England has fallen by a remarkable 60%, with accelerated reductions in annual age adjusted death rates since 2000. However, as I discussed in chapter 2, CHD remains the leading cause of mortality and is a major contributor to social inequalities in premature mortality in England. Moreover, UK death rates have fallen faster in the most socially advantaged groups compared to the most deprived, as I shown in the previous section. Thus, although absolute inequalities in mortality have fallen, relative inequalities have increased over the last decade.

Previous country-level analyses have suggested that about 50%-70% of the dramatic falls in CHD mortality between 1980 and 2000 were explained by improvements in modifiable risk factors (mainly smoking, total cholesterol and blood pressure), with the remaining 30% -50% being attributable to improved uptake of evidence-based treatments.[144,149,319] However, so far no study has examined the specific contribution of risk factors and medical treatments to the underlying social differentials in CHD mortality falls. This might help to shed further light on the different dynamics showed by CHD mortality trends across the socio-economic spectrum.

The most recent IMPACT study in the UK modelled CHD mortality change in England and Wales between 1981 and 2000.[149] However, since then several initiatives have been rolled-out to improve the delivery of health care in England. These notably include the National Service Framework for CHD (2000), and also the Qualities and Outcome Framework (2004) which aims to monitor and incentivise improvements in the quality of services provided for CHD prevention, diagnosis, treatment and rehabilitation.[320,321] In addition, important population-wide public health measures to reduce risk factors across the entire population have been introduced since 2000. These included the ban on tobacco advertising (2003); comprehensive smoke free legislation (2007), and voluntary agreements to reduce salt and artificial trans-fats in processed food.[322,323] Furthermore, reducing health inequalities was at the heart of New Labour's health agenda when it came to office in 1997.

However, the target to reduce the inequality gap in life expectancy by 2010 was not met.[324] Moreover, the potential effect of population-wide interventions on reducing inequalities in CHD mortality (when compared with individual treatments) remains unclear.[165]

Thus although the following analysis covers a relatively short period of time, the period included a range of measures specifically aimed to improve outcomes and reduce social inequalities. Furthermore, I have quantified the variation by socioeconomic circumstances (SEC) in the relative contributions of modifiable population-level risk factors and evidence-based individual treatments to the fall in CHD mortality during the period 2000 to 2007. To do this I used the widely- replicated IMPACT model, after colleagues had substantially extended the model to quantify socioeconomic inequalities concealed within the overall national trends.

7.4.2 Methods

IMPACTSEC model and data sources

IMPACT is an epidemiological model used to explain the contributions of population-level risk factor changes (incidence reduction) and uptake of evidence-based treatments (case fatality reduction) to the change in CHD deaths between two points in time. This deterministic, cell based model has been described in chapter 6 and elsewhere.[144,149] The extended IMPACTSEC model included all the major risk factors for CHD: smoking, systolic blood pressure, total cholesterol, body mass index (BMI), diabetes, physical inactivity, along with fruit and vegetable consumption; plus all 45 medical and surgical treatments currently in use in nine patient groups. The model included the total population of England aged 25 and over in 2000 and 2007.

Data sources specific to the England population were used to construct the IMPACTSEC model. When several sources were available, we chose the most up-to-date, representative dataset which we could link to a small-area deprivation index. Population estimates and CHD death counts (2000: ICD9 410-414; 2007: ICD10 I20-I25) by sex, five-year age bands to age 85+ and deprivation quintile were obtained from the Office for National Statistics. Emergency admissions for acute myocardial infarction were extracted from Hospital Episode Statistics and supplemented with data from the Myocardial Ischemia National Audit Project to disaggregate ST-elevated acute myocardial infarction and non-ST elevated acute coronary syndrome, and to apportion treatment uptake to each group. For heart failure admissions, the National Health Service (NHS) Heart Failure Survey was used to estimate in-hospital treatment uptake. The General Practice Research Database and the

Health Survey for England provided data on treatment uptake in the community. Risk factor trend data came from the Health Survey for England.

Detailed information on the IMPACTSEC model, calculation methods and data sources are provided in Appendix A4

Stratifying data according to socioeconomic circumstances

Only the Health Survey for England consistently recorded individual socioeconomic position; but all data sources recorded individual postcode of residence. We therefore used a measure of relative area deprivation as a proxy indicator of the socioeconomic circumstances of individuals living in small areas (n=32,482; average population of 1,500). We used the Index of Multiple Deprivation 2007[311] to rank all lower super output areas in England in ascending order of increasing deprivation and grouped them into equal quintiles. Based on postcode of residence, the data providers matched CHD deaths and treated patients to their corresponding deprivation quintile before releasing the data to us.

Deaths prevented or postponed (DPP)

The total number of deaths prevented or postponed (DPP) for each deprivation quintile were calculated as the difference between observed deaths in 2007 and expected deaths had age-, sex- and quintile -specific CHD mortality rates in 2000 remained unchanged. DPPs explained by the model could be positive (i.e. deaths averted) or negative (i.e. additional deaths in 2007 relative to 2000). Any shortfalls between the DPP explained by the model and the total DPPs for each SEC were assumed to reflect either imprecision in our model parameters or omission of other, unmeasured risk factors.

Mortality reductions attributable to treatment uptake

The treatment component of IMPACTSEC included nine mutually exclusive CHD patient groups (Table 7-6). A total of 45 patient treatment-pairings were generated. To avoid double counting of patients treated for two or more conditions within the year (e.g. heart failure develops within 1 year after myocardial infarction in approximately 30% of survivors) we quantified overlaps between different groups and made appropriate adjustments (Appendix A4).

The numbers eligible for treatment, uptake of specific treatment, one year case fatality rates, and relative risk reduction due to treatment, all stratified by age, sex and CHD subgroup, were

extracted from relevant data sources (See Appendix A4). Disease prevalence and treatment uptake were further stratified by deprivation quintiles.

Deaths prevented by each intervention were then calculated by multiplying the numbers of patients in each diagnostic group by the proportion of those patients who received the treatment, the baseline case fatality rate, and the relative risk reduction of that treatment. To estimate the cumulative effect of relative risk reduction for patients on a combination of drug therapies, we used the Mant and Hicks correction.[276]

Many of the treatments were already widely used in 2000. The net benefit of an intervention in 2007 was therefore calculated by subtracting the expected number of deaths prevented if 2000 uptake rates had remained unchanged from the deaths prevented using 2007 treatment uptake rates.

We assumed that adherence (i.e. the proportion of eligible patients actually taking therapeutically effective levels of medication) was 100% among hospitalised patients, 70% among symptomatic patients in the community, and 50% among asymptomatic patients in the community.[144]

Mortality reductions attributable to risk factor changes

We included seven risk factors in the model; both behavioural –smoking, physical inactivity, fruit and vegetable consumption, BMI – and physiological markers including systolic blood pressure, total serum cholesterol and diagnosed diabetes. To quantify the mortality benefits of an absolute change in each specific risk factor between 2000 and 2007, we used two approaches: a regression-based approach for factors measured on a continuous scale (e.g. total blood cholesterol); and, a population-attributable risk fraction approach for dichotomous variables such as diagnosed diabetes. The independent regression coefficients of mortality benefit for a unit change in mean risk factor were obtained from published multivariate analyses (Appendix A4). Hence, the contribution of each risk factor to deaths averted was then calculated as the product of the deaths in 2000 (the base year), the absolute change in risk factor, and the associated relative risk reduction. For binary variables, we used relative risks from the Interheart Study (see Appendix A4)

We assumed that there was no further synergy among risk factors nor between the treatment and risk-factor components of the model. Lag times between the change in cardiovascular risk factor levels and change in CHD mortality rates were assumed to be relatively rapid and were therefore not

specifically modelled. We used a different approach to estimate uncertainty for this version of the IMPACT model. We calculated 95% uncertainty intervals around the model output (i.e. DPPs) were calculated using Monte Carlo simulation. This involved replacing all fixed input parameters used in the model by appropriate probability distributions, and repeatedly recalculating the model output with values sampled from the defined input distributions (See Appendix A4). We used the EXCEL add-in Ersatz (www.epigear.com) to perform 1000 runs to determine using an bootstrapping approach the 5 and 95 percentiles of the resulting output distribution of DPPs values. These provided the 95% uncertainty intervals reported.

7.4.3 Results

Between 2000 and 2007, the age standardised CHD mortality rate in adults aged 25 and over fell from 229 to 147 deaths per 100,000; a decline of 36% overall or 6.1% per year (see appendix A3). In 2007, there were 74,174 CHD deaths, 56% of these were in men. Both death rates and the number of deaths were lowest in the most affluent quintile and the pace of fall was also faster: decreasing by 6.7% per year compared to just 4.9% in the most deprived quintile. This therefore widened relative inequalities over the period.

Nationally, there were 38,070 fewer CHD deaths in 2007 than if 2000 mortality rates had persisted. This represents the total number of deaths prevented or postponed (DPPs). Despite the slower annual rates of fall in the most deprived quintile, their higher CHD mortality rates in the base year meant that the number of DPPs by 2007 were fairly equally distributed: about 6,560 fewer deaths in the most deprived quintile versus 7,355 in the most affluent.

Overall, approximately half of the total CHD mortality fall (19,780 fewer deaths or 52%, minimum 15%, to maximum, 120%) was attributable to improvements in uptake of medical and surgical treatments (Table 7-6) with population-level risk factor changes accounting for approximately 14,250 (37%, 21% to 58%)fewer deaths (Table 7-7). The model could not explain some 10% of the overall mortality fall (i.e. a shortfall of 4,040 deaths) (Figure 7-14, Table 7-7). The contribution of medical treatments to the deaths averted was very similar across all quintiles, ranging from 50% in the most affluent quintile to 53% in the most deprived (Table 7-8). But risk factor changes explained a smaller proportion of deaths prevented in the most affluent quintile compared with the most deprived (approximately 31% versus 49%, respectively). As a result, about 19% of CHD deaths prevented could not be explained by the model in the most affluent quintile. The

proportion not explained fell successively with increasing deprivation; the model predicted 115 more deaths prevented (or -2%) than the total DPPs for the most deprived quintile.

The most substantial contribution to deaths prevented by treatments came from statin treatment for hyperlipidemia (-14% of the total mortality reduction), management of chronic stable coronary artery disease (-13%) and secondary prevention following myocardial infarction or revascularisation (-11%) (Table 7-6). Uptake rates of statins and angiotensin-converting enzyme inhibitors (ACE inhibitors) or angiotensin receptor blockers (ARB) more than doubled for secondary prevention and the management of stable coronary artery disease (Table 7-9).

Figure 7-12 Proportion of the CHD mortality fall explained by risk factors or treatments, by deprivation quintile, England 2000-2007

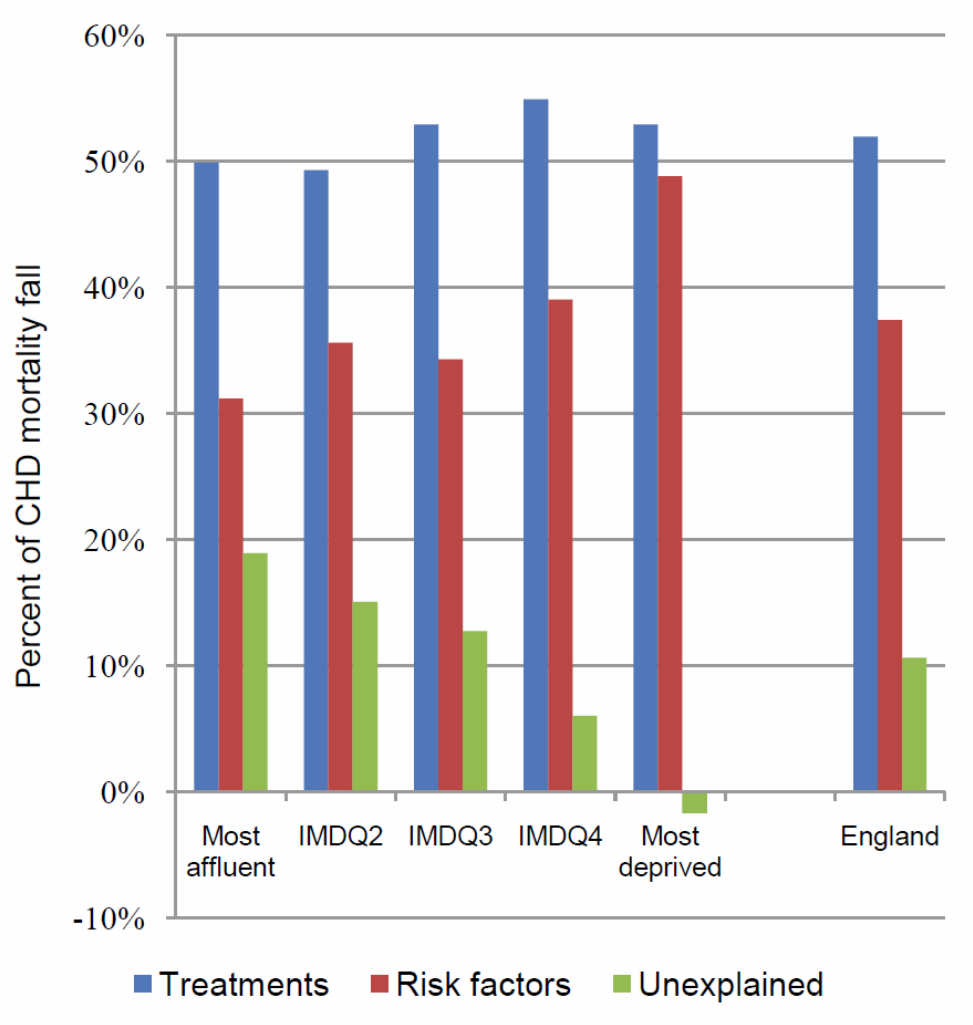


Table 7-6 CHD deaths prevented or postponed due to changes in treatment uptake between 2000 and 2007 in England and stratified by deprivation quintiles

Patient Group	Deaths Prevented or Postponed				By IMD: Deaths Prevented or Postponed				
	Eligible n	Best,%	Min,%	Max,%	Most Affluent,n	IMDQ2, n	IMDQ3, n	IMDQ4, n	Most Deprived, n
STEMI	***-130***	***-0.3***	***-0.7***	***-0.5***	***-6***	***-27***	***-28***	***-31***	***-38***
Thrombolysis	-118				-22	-23	-21	-23	-29
Aspirin	24				5	4	5	3	7
B-Blocker	4				1	0	1	1	2
ACE inhibitor or ARB	5				0	0	2	1	2
Clopidogrel	65				12	14	14	13	12
Primary PCI	139				30	28	28	27	25
Primary CABG	1				0	0	0	0	0
CPR in hospital	-252				-33	-51	-57	-53	-57
NSTEACS	***295***	***0.8***	***0.1***	***2.1***	***57***	***59***	***62***	***53***	***65***
Aspirin and heparin	341				54	68	68	63	88
Aspirin alone	-114				-15	-24	-21	-21	-31
PG IIB/IIIA inhibitors	-1				-2	-1	0	0	2
ACE inhibitor or ARB	44				6	8	9	10	10
B-Blocker	27				5	5	6	5	6
Clopidogrel	203				36	40	46	41	40
CABG surgery	1				2	1	0	0	-1
PCI	54				11	10	12	12	10
CPR in hospital	-259				-40	-48	-58	-55	-58
Secondaryprevention post MI	***3510***	***9.2***	***7.3***	***11.7***	***640***	***775***	***746***	***711***	***639***
Aspirin	351				65	69	76	87	55
B-Blocker	862				158	197	194	167	146
ACE inhibitor or ARB	903				166	200	190	175	172
Statin	1303				241	280	269	268	245
Warfarin	92				8	30	17	15	21
Rehabilitation	0				0	0	0	0	0

Table 7-6 (continued)

Patient Group	Deaths Prevented or Postponed				By IMD: Deaths Prevented or Postponed				
	Eligible n	Best,%	Min,%	Max,%	Most Affluent,n	IMDQ2, n	IMDQ3, n	IMDQ4, n	Most Deprived, n
Secondaryprevention post MI	***3510***	***9.2***	***7.3***	***11.7***	***640***	***775***	***746***	***711***	***639***
Aspirin	351				65	69	76	87	55
B-Blocker	862				158	197	194	167	146
ACE inhibitor or ARB	903				166	200	190	175	172
Statin	1303				241	280	269	268	245
Warfarin	92				8	30	17	15	21
Rehabilitation	0				0	0	0	0	0
Secondary prevention post revascularisation	***590***	***1.5***	***1.2***	***1.9***	***112***	***121***	***128***	***117***	***110***
Aspirin	45				10	10	11	8	7
B-Blocker	154				29	31	34	31	30
ACE inhibitor or ARB	179				35	37	37	34	36
Statin	174				31	36	38	37	32
Warfarin	0				0	0	1	0	-1
Rehabilitation (post CABG)b	0				0	0	0	0	0
Rehabilitation (post PCI)	36				7	7	7	7	7
Chronic stable CAD	***4835***	***12.7***	***9.8***	***17.2***	***851***	***1007***	***1015***	***1006***	***955***
Aspirin in community	818				139	159	176	179	165
Statins in community	2488				443	523	526	510	485
ACE inhibitor or ARB	1292				241	281	268	261	241
CABG surgery	236				27	44	45	57	63

Table 7-6 (continued)

Patient Group	Deaths Prevented or Postponed				By IMD: Deaths Prevented or Postponed				
	Eligible n	Best,%	Min,%	Max,%	Most Affluent,n	IMDQ2, n	IMDQ3, n	IMDQ4, n	Most Deprived, n
Heart failure - hospital	***250***	***0.7***	***0.5***	***0.8***	***42***	***47***	***53***	***59***	***51***
ACE inhibitor	49				8	9	10	10	11
B-Blocker	39				6	8	8	9	9
Spironolactone	37				6	7	8	8	8
Aspirin	126				21	22	27	32	23
Heart failure - community	***3335***	***8.8***	***7.3***	***10.6***	***564***	***689***	***732***	***711***	***641***
ACE inhibitor or ARB	737				125	158	171	146	137
B-Blocker	1592				284	325	353	338	292
Spironolactone	617				105	134	120	129	129
Aspirin	389				50	72	88	97	83
Hypertension treatment	***1800***	***4.7***	***1.8***	***10.7***	***357***	***411***	***408***	***345***	***277***
Hyperlipidemia treatment (statins)	***5300***	***13.9***	***5.3***	***30.8***	***1054***	***975***	***1305***	***1194***	***772***
A:Total treatment contribution	***19780***	***52.0***	***41.4***	***70.8***	***3670***	***4055***	***4420***	***4166***	***3471***

Eligible patient numbers rounded to nearest 5.

ARB: Angiotensin receptor blocker; ACE inhibitor: angiotensin-converting enzyme inhibitors; B-blocker: beta-blocker; CABG: coronary artery bypass graft; CAD: coronary artery disease; CPR: cardiopulmonary resuscitation; DPP: deaths prevented or postponed; IMD: index of multiple deprivation; NSTEACS: Non-STelevation acute coronary syndrome; MI: myocardial infarction; PCI: percutaneous coronary intervention; PG: platelet glycoprotein; STEMI: ST elevation myocardial infarction.

Table 7-7 CHD deaths prevented or postponed due to changes in risk factor prevalence between 2000 and 2007 in England and stratified by deprivation quintile

	England: Deaths Prevented or Postponed				By IMD: Deaths Prevented or Postponed				
			Min	Max	Most Affluent	IMDQ2	IMDQ3	IMDQ4	Most Deprived
	Number	%	%	%	Number				
Current smoking	1440	3.8	-3.5	12.0	141	204	28	319	489
Diabetes	-3595	-9.4	15.4	-3.1	-467	-562	-681	-728	1159
Physical inactivity	540	1.4	1.1	1.7	81	98	107	117	140
Systolic blood pressure, mmHg [a]	12475	32.8	19.5	45.3	2062	2407	2587	2672	2749
Total cholesterol, mmol/l [b]	2365	6.2	10.8	15.7	260	556	331	392	824
Body mass index	-705	-1.8	-3.3	-0.4	-120	-140	-147	-145	-149
Fruit and vegetable consumption	1725	4.5	1.1	9.3	336	369	379	334	308
Total risk factors contribution	*14250*	*37.4*	*14.1*	*57.3*	*2293*	*2930*	*2864*	*2960*	*3202*
Total treatment contribution [c]	*19780*	*52.0*	*41.4*	*70.8*	*3670*	*4055*	*4420*	*4166*	*3471*
DPPs explained by the model	*34030*	*89.4*	*72.7*	*107.6*	*5963*	*6986*	*7284*	*7126*	*6673*
DPPs not explained	*4040*	*10.6*			*1390*	*1239*	*1065*	*458*	*-115*
Total DPPs	*38070*	*100*			*7353*	*8225*	*8349*	*7584*	*6558*

[a] After subtracting deaths prevented or postponed (DPPs) due to hypertension treatment in primary prevention.

[b] After subtracting DPPs due to statins treatment in primary prevention.

These two therapies together contributed some 6,340 DPPs (17%). In contrast, deaths averted due to changes in treatment uptake in hospital-based patient groups were relatively modest: contributing just 65 fewer deaths (-0.5%) amongst emergency admissions for infarction and unstable angina (ST elevation myocardial infarction (STEMI) and non-ST elevation acute coronary syndrome (NSTEACS), respectively). Improved heart failure treatments in the community resulted in approximately 3,335 fewer deaths, with relatively modest gains (250 fewer deaths) in hospitalised patients. Furthermore, there were essentially no gradients in treatment uptake across deprivation quintiles for either hospital treatment or drugs prescribed in the community for secondary prevention and heart failure (Table 7-9).

Of the deaths prevented due to population-level risk factor changes, the largest contribution came from the fall in systolic blood pressure amongst those not on hypertensive medications (approximately 12,475 fewer deaths, or 33%) (Table 7-7). On the other hand, gains from hypertensive medication were modest (approximately 1,800 fewer deaths, 5%) (Table 7-6). Blood pressure falls were twice as high in women (5.4 mmHg versus 2.5 mmHg in men) but were of a similar magnitude across all deprivation quintiles (Table 7-10). Both in terms of absolute numbers and proportions, more deaths were prevented due to blood pressure falls in the most deprived quintile than in the most affluent (Table 7-7 and 7-8).

In contrast, the benefits attributable to statins lowering of total cholesterol levels were double those attributable to the fall in cholesterol levels in the population not on treatment (approximately 5,300 versus 2,365 fewer deaths, respectively). Between 2000 and 2007, hyperlipidaemia treatment increased nine-fold across all social groups from 1% to 9% (Table 7-9). Amongst those not on statins treatment, total cholesterol levels fell marginally more in women than men and by a similar magnitude across deprivation quintiles (Table 7-10). Thus, while the proportionate fall in deaths attributable to cholesterol reduction in the general population was similar across quintiles, in absolute terms more deaths were prevented in the most deprived quintiles (Table 7-7).

Mortality gains due to positive trends in smoking, fruit and vegetable consumption and physical activity risk factors were negated by increases in BMI and diabetes (together contributing 4,300 additional deaths, equivalent to an 11% increase in mortality) (Table 7-7). Favourable trends in smoking, fruit and vegetable consumption and physical activity were modest; together only contributing about 10% of the overall mortality fall (Table 7-7). Smoking prevalence declined in men and women by a similar amount (4%); however, there was a clear social gradient with larger absolute falls in smoking prevalence in more deprived quintiles (Table 7-10). Furthermore, levels of smoking still remained twice

as high in the most deprived compared to affluent groups (see Appendix 1A4). Physical inactivity fell more in men (7%) than women (4%) across all deprivation quintiles; however three in four adults remained classed as inactive in every quintile.

Even over the relatively short period of this analysis, the social gradient in diabetes became more pronounced resulting in three times as many additional diabetes-related deaths in the most deprived quintile compared with the most affluent.

Risk factors explained 23.0% of the fall in young men (aged 25-54) in the least deprived quintile, compared to 30.6% in the most deprived. Treatments explained 19.2% in the least deprived and 25.9% in the same age group. Similar patterns were noted in older men, although patterns in women are more difficult to interpret. Risk factors explained more of the decline in young affluent women, although the model consistently overestimate, because of the small number of DPPs expected in these age groups. (Table 7-11)

Model fit and sensitivity analysis

The percentage unexplained by the model varied by age, sex and socioeconomic circumstances. The model fit was generally good overall and in women and men living in the most deprived areas. However, the fit was less good in affluent areas, where the DPPs explained by the model were significantly lower than the observed DPPs (the 95% uncertainty intervals did not overlap the observed DPPs for IMDQ1. (See Appendix A4). Model fit also varied substantially by gender, being better for women than men (Appendix A4), and in older adults.

Table 7- 8 Comparative percentage distribution of deaths prevented or postponed by deprivation quintile

	England,%	Most Affluent,%	IMDQ2,%	IMDQ3,%	IMDQ4,%	Most Deprived,%
Treatments:						
STEMI	-0.3	-0.1	-0.3	-0.3	-0.4	-0.6
NSTEACS	0.8	0.8	0.7	0.7	0.7	1.0
Secondary prevention post MI	9.2	8.7	9.4	8.9	9.4	9.7
Secondary prevention post revascularization	1.5	1.5	1.5	1.5	1.5	1.7
Chronic stable CAD	12.7	11.6	12.2	12.2	13.3	14.6
Heart failure in the hospital	0.7	0.6	0.6	0.6	0.8	0.8
Heart failure in the community	8.8	7.7	8.4	8.8	9.4	9.8
Hypertension treatment	4.7	4.9	5.0	4.9	4.5	4.2
Hyperlipidemia treatment (statins)	13.9	14.3	11.9	15.6	15.7	11.8
Total treatments	***52.0***	***49.9***	***49.3***	***52.9***	***54.9***	***52.9***
Risk factors:						
Smoking	3.8	1.9	2.5	3.4	4.2	7.5
Diabetes	-9.4	-6.4	-6.8	-8.2	-9.6	-17.7
Physical inactivity	1.4	1.1	1.2	1.3	1.5	2.1
Systolic blood pressure, mmHg	32.8	28.0	29.3	31.0	35.2	41.9
Total cholesterol, mmol/l	6.2	3.5	6.8	4.0	5.2	12.6
Body Mass Index	-1.8	-1.6	-1.7	-1.8	-1.9	-2.3
Fruit and vegetable consumption	4.5	4.6	4.5	4.5	4.4	4.7
Total Risk Factors	***37.4***	***31.2***	***35.6***	***34.3***	***39.0***	***48.8***
DPPs explained by model	89.4	81.1	84.9	87.2	94.0	101.7
DPPs not explained by model	10.6	18.9	15.1	12.8	6.0	-1.8
DPPs Counts						
DPPs explained by model	34030	5963	6986	7284	7126	6673
due to treatment uptake	19780	3670	4055	4420	4166	3471
due to risk factor change	14250	2293	2930	2864	2960	3202
DPPs unexplained by model	4040	1390	1239	1065	458	-115
Total DPPs	38070	7355	8225	8350	7585	6555

Table 7-9 Percentage treatment uptake rates in 2000 and 2007 for England and stratified by deprivation quintile

Patient Group	Eligible Patients	England		Most Affluent		IMDQ2		IMDQ3		IMDQ4		Most Deprived	
		2000	2007	2000	2007	2000	2007	2000	2007	2000	2007	2000	2007
STEMI	***20,700***												
Thrombolysis		77.2	56.7	79.4	58.6	77.9	59.5	75.4	57.1	76.2	56.0	77.4	52.5
Aspirin		93.6	96.0	93.6	96.6	94.7	96.3	93.1	95.4	93.2	95.6	93.4	96.4
B-Blocker		71.3	70.3	74.8	70.9	72.3	69.1	71.0	69.8	69.6	69.5	69.9	72.4
ACE inhibitor or ARB		77.2	76.3	79.8	76.6	78.9	75.6	75.4	75.5	75.4	74.8	77.3	79.2
Clopidogrel		27.7	88.5	26.9	88.7	25.7	87.7	28.0	88.4	28.5	88.4	28.9	89.2
Primary PCI		3.9	23.7	2.9	24.2	3.4	21.8	3.8	23.3	4.3	24.5	4.8	24.8
Primary CABG		0.1	0.1	0.1	0.1	0.0	0.1	0.1	0.1	0.1	0.2	0.0	0.1
CPR in hospital		11.4	6.6	9.9	6.5	11.6	7.1	11.7	6.3	11.8	6.7	11.6	6.3
NSTEACS	***91,285***												
Aspirin and heparin		64.0	79.7	67.1	79.7	65.0	80.3	66.7	79.9	65.7	80.2	57.9	78.8
Aspirin alone		24.2	12.8	21.5	13.5	23.9	12.3	21.5	12.7	23.5	12.6	28.9	13.1
PG IIB/IIIA		6.1	5.8	9.4	6.2	7.3	5.8	6.1	5.1	4.7	5.2	4.3	6.8
ACE inhibitor or ARB		66.0	73.2	68.6	73.1	64.5	72.2	65.9	72.5	64.3	72.7	67.0	75.0
B-Blocker		63.2	67.6	66.1	68.2	62.7	67.7	63.5	66.7	61.7	66.3	62.8	69.2
Clopidogrel		44.3	86.6	43.5	87.1	44.2	86.9	42.3	86.8	45.6	85.9	45.4	86.3
CABG surgery		3.0	2.6	3.5	3.4	3.2	2.7	3.2	2.6	2.9	2.3	2.5	2.1
PCI		3.1	6.7	3.6	7.7	3.4	6.9	3.2	7.0	2.9	6.4	2.5	5.7
CPR in hospital		5.3	2.3	4.6	2.3	4.9	2.2	5.3	2.1	5.6	2.5	5.8	2.5
Secondary prevention post revascularisation	***111,930***												
Aspirin		64.3	76.5	58.8	73.5	63.5	76.2	62.5	76.5	65.7	76.1	71.2	80.0
B-Blocker		30.7	55.7	29.2	52.7	30.5	55.6	29.8	56.4	31.7	56.9	32.3	56.9
ACE inhibitor or ARB		30.1	64.2	30.8	63.9	29.2	63.0	29.5	63.9	30.9	63.4	30.5	67.1
Statin		58.2	84.5	61.7	85.1	58.2	84.6	56.3	83.9	56.3	84.8	58.7	84.2
Warfarin		7.4	6.7	7.9	7.2	7.3	6.6	6.7	6.5	7.1	7.1	7.9	6.1
Rehabilitation (post CABG)		73.0	73.0	73.0	73.0	73.0	73.0	73.0	73.0	73.0	73.0	73.0	73.0
Rehabilitation (post PCI)		10.0	20.0	10.0	20.0	10.0	20.0	10.0	20.0	10.0	20.0	10.0	20.0

Table 7-9 (continued)

	Eligible	England		Most Affluent		IMDQ2		IMDQ3		IMDQ4		Most Deprived	
	xPatients	2000	2007	2000	2007	2000	2007	2000	2007	2000	2007	2000	2007
Secondary prevention post MI	***565,595***												
Aspirin		59.7	74.4	56.4	72.4	60.0	74.3	59.2	74.5	58.8	74.8	63.3	75.8
B-Blocker		32.6	53.4	34.0	54.0	34.0	54.6	31.6	53.3	32.2	52.9	31.7	52.4
ACE inhibitor or ARB		31.3	62.0	32.3	62.6	32.5	62.3	31.0	61.6	30.6	61.2	30.5	62.5
Statin		37.1	77.4	39.8	77.9	39.5	77.8	35.9	76.6	34.7	76.6	36.2	78.1
Warfarin		6.6	8.1	7.7	8.3	6.7	8.9	6.5	7.9	6.2	7.7	6.2	7.6
Rehabilitation		45.0	45.0	45.0	45.0	45.0	45.0	45.0	45.0	45.0	45.0	45.0	45.0
Chronic stable CAD	984,805												
Aspirin in community		42.9	62.4	38.7	57.2	42.6	61.4	44.7	64.3	42.9	63.4	45.0	65.3
Statins in community		23.9	66.2	25.4	63.4	24.2	65.4	23.7	66.5	23.0	66.3	23.3	69.2
ACE inhibitor or ARB		19.8	45.7	19.9	45.1	19.0	45.5	20.5	45.8	20.1	45.5	19.7	46.5
CABG surgery		8.7	9.6	8.8	9.8	8.7	9.7	9.6	10.3	8.7	9.7	7.7	8.8
Heart failure - hospital	***24,625***												
ACE inhibitor		53.2	59.1	51.8	57.6	52.1	57.9	52.7	58.6	53.4	59.4	55.2	61.4
B-Blocker		25.4	28.2	24.3	27.0	24.5	27.2	25.0	27.8	25.6	28.5	27.1	30.1
Spironolactone		20.7	22.9	19.8	22.0	20.0	22.3	20.4	22.7	20.8	23.1	21.8	24.3
Aspirin		59.2	73.9	56.6	71.9	59.8	73.3	58.6	74.1	58.1	75.3	62.2	74.4
Heart failure - community	***172,770***												
ACE inhibitor or ARB		45.6	68.9	48.2	70.2	44.5	69.3	43.4	67.8	45.9	69.2	46.6	68.4
B-Blocker		10.4	34.2	10.7	35.1	11.2	34.6	10.8	34.9	9.4	34.2	10.1	32.4
Spironolactone		3.9	14.5	4.3	14.7	3.9	14.9	3.6	13.0	3.9	15.1	4.0	14.9
Aspirin		38.1	50.4	37.9	46.3	38.3	49.9	37.3	50.3	37.0	51.8	40.0	52.7
Hypertension treatment	35,280,845	8.3	13.5	8.3	14.0	8.2	13.8	8.6	13.9	8.2	13.0	8.3	12.7
Hyperlipidemia treatment	35,280,845	1.1	9.0	1.0	7.9	1.1	8.5	1.1	9.1	1.4	10.3	1.3	9.1

Table 7-10 Absolute change in risk factor levels between 2000 and 2007 for England and stratified by deprivation and sex.

	Overall levels		Absolute change in percentage points, 2000 to 2007					
	2000a	2007a	England	Most Affluent	IMDQ2	IMDQ3	IMDQ4	Most Deprived
Smoking prevalence (%)								
Male	27.2	23.6	-3.7	-2.6	-3.1	-3.6	-4.1	-4.8
Female	23.4	19.9	-3.5	-2.5	-3.0	-3.4	-4.0	-4.6
Diabetes prevalence (%)								
Male	3.7	6.5	2.8	2.4	2.7	2.8	2.6	3.6
Female	2.9	4.8	1.9	1.6	1.4	1.6	2.1	2.8
Physical inactivity (%)								
Male	80.9	74.0	-6.9	-6.9	-6.7	-6.8	-6.9	-7.2
Female	82.4	78.1	-4.3	-4.3	-4.2	-4.2	-4.2	-4.4
Systolic blood pressure (mmHg)								
Male	133.1	130.6	-2.5	-2.6	-2.6	-2.5	-2.5	-2.4
Female	131.0	125.6	-5.4	-5.3	-5.5	-5.5	-5.5	-5.5
Total cholesterol (mmol/L)								
Male	5.6	5.4	-0.1	-0.2	-0.2	-0.2	-0.1	-0.1
Female	5.7	5.5	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2
Body mass index (kg/m2)								
Male	27.3	27.7	0.4	0.4	0.4	0.4	0.3	0.3
Female	26.9	27.2	0.2	0.2	0.2	0.2	0.2	0.3
Fruit & vegetable consumption (portions)								
Male	3.4	3.7	0.4	0.4	0.4	0.4	0.4	0.3
Female	3.6	4.0	0.4	0.4	0.4	0.4	0.4	0.4

Notes: See appendix A4 for weighted averages of risk factor levels for each deprivation quintile, 2000 and 2007

Table 7-11 Comparative percentage distribution of deaths prevented of postponed, by deprivation, gender and age.

	IMDQ1		IMDQ2		IMDQ3		IMDQ4		IMDQ5	
					Model DPPs					
	Dpps	**%**	**Dpps**	**%**	**Dpps**	**%**	**Dpps**	**%**	**Dpps**	**%**
Treatments										
M 25-54	36	19.2%	56	26.4%	40	21.7%	59	24.8%	72	25.9%
M 55-74	549	33.5%	671	34.6%	609	29.1%	620	31.1%	643	34.0%
M 75-84	759	46.1%	892	53.5%	880	49.4%	795	54.1%	663	54.8%
F 25-54	18	87.2%	17	62.6%	14	21.6%	24	38.4%	35	33.6%
F 55-74	267	43.7%	356	43.0%	383	42.8%	431	47.3%	397	39.2%
F 75+	699	54.3%	682	52.2%	856	61.2%	923	68.8%	654	61.3%
Risk factors										
M 25-54	44	23.0%	48	22.7%	52	28.1%	68	28.6%	85	30.6%
M 55-74	726	44.2%	886	45.6%	973	46.4%	978	49.0%	1018	53.9%
M 75-84	588	35.7%	610	36.6%	591	33.2%	603	41.0%	475	39.3%
F 25-54	15	72.2%	19	69.6%	30	46.5%	38	60.4%	53	50.7%
F 55-74	423	69.2%	555	67.1%	641	71.6%	671	73.7%	822	81.3%
F 75+	834	64.8%	1009	77.2%	1069	76.4%	1043	77.8%	909	85.3%
					Observed DPPs					
M 25-54	189		213		184		236		277	
M 55-74	1640		1941		2094		1995		1890	
M 75-84	1646		1666		1780		1471		1210	
	3475		3820		4059		3703		3377	
F 25-54	21		27		64		63		104	
F 55-74	611		828		896		911		1012	
F 75+	1288		1307		1400		1341		1066	
	1920		2162		2360		2316		2182	
M+F	5395		5982		6418		6018		5559	

7.4.4 Interpretation

Between 2000 and 2007, English coronary heart disease mortality rates fell by an impressive 36% resulting in approximately 38,000 fewer CHD deaths in 2007. However the relative mortality inequalities between rich and poor persisted and even increased slightly over this period. This is the first study to analyse the socioeconomic components concealed within the overall mortality reductions attributable specifically to risk factor trends and to evidence-based treatments. By using deprivation scores for area of residence as a unified marker of socioeconomic circumstances across all relevant large databases of population health and health service use in England, the study had adequate statistical size to quantify the impact of changes in risk factors and treatments within socioeconomic groups, even over a relatively short period of seven years. Understanding these recent trends, and their socially divergent trajectories, will be crucial to planning the most effective and equitable future strategies to prevent cardiovascular disease and reduce inequalities.

Approximately half the fall in CHD mortality was attributable to increased medical therapies. These benefits largely reflected a doubling of drug use for community patients with chronic disease (who represent the largest CHD burden). In contrast, the contribution of medical interventions in hospital was relatively modest. Firstly, because the numbers of patients with acute disease were much smaller. Secondly, because few new treatments were subsequently introduced other than clopidogrel and primary angioplasty. And thirdly, the uptake rates for existing treatments were already close to maximum levels in 2000. The age-specific prevalence of CHD is socially graded. With similar levels of uptake of treatments across socioeconomic quintiles in both base and final years, this meant that the benefits of increased treatment were distributed remarkably evenly across social groups, which suggests a fairly equitable distribution of therapies across the NHS.

Reductions in major cardiovascular risk factors explained approximately half the fall in CHD mortality (49%). However, the net benefit much was much smaller (approximately 37%) because adverse trends in BMI and diabetes potentially increased mortality by some 10%.

The single largest contribution to the overall CHD mortality decrease came from population falls in blood pressure with relatively small gains from hypertension therapies.[325]

Furthermore, reductions were similar across social groups. This is therefore entirely consistent with recent UK population-wide reductions in salt intake[64,326], and with recent encouraging trends in other wealthy counties. Small increases in fruit and vegetable consumption and physical activity were seen across all social groups. Furthermore, moderate declines in smoking levels were actually greater in deprived areas. This may reflect the benefit of cumulative tobacco control policies since 2000, reinforced by the targeting of cessation services in deprived areas.[327]

However, after excluding the effect of statins therapy, the decline in cholesterol levels in the wider population was modest. This may well reflect a failure to implement more effective policies.[328] Particularly worrying was the approximately 4000 additional deaths attributable to the continuing rises in diabetes and BMI. This is consistent with recent Foresight analyses and represents a further warning to policy makers.[329]

The absolute gap in CHD mortality between the most affluent and most deprived groups narrowed over the period of our study, however relative inequalities widened. This was unlikely to be due to differential treatment of diagnosed patients because levels of uptake of evidence-based therapies were similar for all groups. The pace of fall in mortality in the most affluent groups was faster; but changes in risk factor levels could not explain about 20% of this fall. Perhaps the most likely explanation for this is a social gradient in effect modification. Thus, the current model assumed that the mortality decrease per unit change in risk factor was similar across deprivation quintiles. However, the benefits of a specific decrease in blood pressure or cholesterol may be disproportionately higher in more affluent groups, perhaps reflecting synergy with other positive trends.[27] A recent cohort analysis found that even if four classic risk factors– blood pressure, cholesterol, smoking and diabetes – were to be completely eliminated in middle-aged men, relative inequalities in CHD mortality between those in low and high employment grades would persist despite a 70% reduction in absolute mortality differences.[330] Furthermore we do not have many estimates of the cumulative benefit associated with a lifetime of low-risk. For example, the Finnish Public Sector Study found that a marked socioeconomic gradient in absolute risk of CHD mortality persisted even in a low-risk sub-group that had never smoked, were not obese or physically inactive and who consumed moderate amounts of alcohol.[331]

Alternative explanations for the fraction of the mortality fall unexplained by the model include the possible omission of more "upstream" risks such as psychosocial stress which might differentially benefit affluent groups.[27,302] Differential levels of adherence to prescribed medications may also play a role: however, this is a relatively under-researched area without clear cut evidence to support or refute the existence of systematic social gradients.[332-334] We also tested the impact of varying adherence rates differentially on the DPPS explained. We found that this had only a small effect on the gradient in the proportion unexplained. Finally, measurement error may contribute; Health Survey estimates of risk factor trends by deprivation quintiles may lack precision because of small samples and differential response rates.

The social gradients by age were not very marked, although in general showed that in more deprived groups, risk factors and treatments explained more of the observed decline, particularly in those under 55 years. THE IMPACT model assumes a linear trend in mortality, so is not entirely appropriate to explain the trend pattern described in section 7.3, which are more complex. However, the relatively shallow gradients by age in the proportion of deaths prevented or postponed are consistent with the lack of clear-cut age patterns in the pace of decline across deprivation quintiles. This also might be the result as well of the modest changes observed in powerful risk factors, like smoking or cholesterol.

Compared with previous IMPACT analyses from a baseline of the 1980s[144,149,196,266,271,335], models of more recent changes, for example in Ontario[319], demonstrate the growing relative contribution from improved treatments to reductions in CHD mortality. However, country-specific proportions attributable to risk factors or treatments are relative to the scale of the decline, and hence potentially misleading. Thus, although Nordic countries possess uniformly good health services, their larger absolute falls in coronary mortality mainly reflect particularly impressive decreases in major risk factors, mainly cholesterol, blood pressure and smoking, and also smaller adverse trends in obesity and diabetes.[148,196]

The IMPACT model has been replicated and validated in diverse national populations. This is the first IMPACT study to quantify the socioeconomic components of the contributions of changes in treatment and risk factors to falls in coronary mortality. The main datasets used are reasonably representative of the socioeconomic distribution of the English population and large enough for reasonably accurate estimates of socioeconomic change.

A number of limitations should also be acknowledged. These include the use of area-level categorisation of socioeconomic circumstances. However, area deprivation correlates well with individual socioeconomic position and may also help to capture the contextual effects of living conditions.[336,337] Approximately ten percent of the CHD mortality fall was not explained by the model. The model fit was also less good in men in affluent areas, as discussed earlier. However, the model fit was generally good overall and in women and in men living in the most deprived areas.

Approximately half of the recent substantial CHD mortality fall in England was attributable to medical therapies. Benefits were relatively even across social groups. This is consistent with equitable service delivery across the NHS. Treatment uptake in hospitals was close to maximum levels over the entire period while follow up treatment of cardiovascular patients in the community substantially improved and was equitable. This suggests the Qualities and Outcome Framework which was being implemented in general practice during the study period was an effective incentive for an effective incentive for improving uptake overall.[338]

However, the net gains from risk factor improvements were small, reflecting modest recent decreases in powerful cardiovascular risk factors such as smoking and cholesterol, and further eroded by continuing rises in BMI and diabetes. This throws a spotlight on recent UK policies for salt reduction and tobacco control (relatively effective) and healthier diets (relatively neglected). Elsewhere, the successful introduction of effective, powerful, rapid and cost-saving policy interventions have achieved substantial reductions in the saturated fat, trans-fats, sugars and calories hidden in processed food, takeaways and sweetened drinks.[148,328] Mandatory interventions involving legislation, regulation, taxation or subsidies consistently appear more effective and cost saving than voluntary schemes.[64,339,340] They also tend to be equitable[165] and surprisingly rapid as I discussed in the Polish natural experiment in chapter 6. The UK now has an equally pressing need for population–wide policy interventions to effectively tackle persistent inequalities in cardiovascular mortality.

7.5 CONCLUSIONS

Comparisons within and between countries can provide potentially valuable insights into possible drivers of inequalities in coronary heart disease. The differing results for England and Scotland are intriguing. These differences may be real or may reflect data artefact arising due to higher levels of selective health migration in deprived areas, misclassification of socioeconomic status or uncertainties in accurately estimating the population structure. Furthermore, the complex interplay of risk factor and treatments trend might also explain the different mortality trend patterns by age and socioeconomic status. A future study to model socioeconomic differentials in trend drivers in the Scottish population would therefore be valuable. That might explore potential socioeconomic differences in the proportion of the trends explained by risk factors and by treatments.

In the final chapter of this thesis, I will summarize the main findings, refine the most plausible hypotheses to explain the sudden and rapid changes in mortality now observed in a range of different populations and settings, and then briefly discuss the public health implications.

8 OVERALL CONCLUSIONS AND PUBLIC HEALTH IMPLICATIONS

8.1 INTRODUCTION

The main findings of my thesis suggest that trends in coronary mortality can demonstrate temporal patterns which are surprisingly dynamic. This is very different to the conventional view.

The recent mortality flattening in young adults seen in countries that had previously experienced the decline phase of the epidemics suggest that favourable trends can change quickly. Happily, the rapid reversals observed in young age groups in the Netherlands and in the entire population in Poland suggest that recovery can also happen very quickly. There is a strong case to attribute these changes mainly to major cardiovascular risk factors, since simultaneous, substantial deterioration of medical care in these countries is implausible. The abrupt decline experienced in Poland from 1990 can be reasonably attributed to a great extent to beneficial dietary and lifestyle changes mediating downstream risk factor levels. The complex socioeconomic trend patterns observed in Scotland and England are also more plausibly attributed to changes in risk factors rather than a marked deterioration in treatment uptakes.

These rapid changes however challenge some aspects of our current understanding of CHD causation, particularly suggesting that the temporal relationship between changes in risk factors and changes in outcomes are probably operating in shorter timescales (years rather than decades), with profound public health implications.

8.2 SUMMARY OF RESULTS

Coronary heart disease can be attributed mostly to classical risk factors and their upstream dietary and lifestyle determinants.

I have discussed in chapters 2 and 3 the evidence base that supports our current understanding of CHD causation. The wide variability observed in coronary heart disease mortality rates cannot be explained mostly by genetic differences, suggesting that environmental exposures during the lifetime are the major causative factors. The atherothrombotic process is well characterized, and the central role of cumulative plaque formation and the development of an active inflammatory and thrombotic environment have been linked to the development of the clinical phase of the disease. The atherosclerotic process has been clearly linked to the cumulative, life course exposure to harmful levels of the major biological risk factors; these are independently associated to coronary heart disease incidence, with clear biological mechanisms and showing consistent effects in different populations. Dietary patterns and specific nutrients are also powerful independent predictors of CHD events, and they might act independently or mediated by downstream biological risk factors. The approaches to control the coronary heart disease burden are based on this risk factor paradigm. This in turn suggests that primordial and primary prevention activities may perhaps represent more powerful strategies that treating patients and reducing case fatality rates. Acute triggers might then play a role by precipitating events in patients with established atherosclerotic lesions.

8.2.1 Rates are not set in stone: dynamics of coronary heart disease mortality rates in England, Scotland, Australia, the Netherlands and Poland

The recent trends for coronary heart disease mortality in younger adults reported in the US, England & Wales, the Netherlands and Scotland UK are disquieting. In England & Wales, the previous falls in age-specific mortality rates appear to be flattening in younger men and women (aged under 55 years). Thus far, rates in older adults continue to decline. In Scotland, a recent period of flattening in young men is also evident. In Australia, the overall decline in age-adjusted CHD mortality rates in Australia since the early 1990s conceals an important change in younger

adults. This recent slowing in the rate of mortality decline is occurring in both men and women aged below 45 years. Interestingly, my analysis of a longer series confirms an earlier observation by Wilson in 1995that hinted at mortality flattening in young Australians.

The adverse trends in some in risk factors rather than deterioration of medical care are the most plausible explanations.

The flattening of the decline in CHD mortality among young Dutch adults in the 1990s is evident. However, the subsequent further decline in mortality rates is reassuring and quite important, mainly because it adds support to the concept that the observed flattening is a real phenomenon and not an artefact of low rates or a trend based on only a few years. The limited data on risk factor trends suggest that they are probably linked to these changes. However, more detailed analyses are urgently needed, and indeed, are currently being undertaken.

The rapid decline in coronary heart disease mortality in Poland after 1990 was a massive natural experiment, with everyone experiencing this decline. The shouldering in Poland in 1990 suggests that this was probably a strong period effect temporally associated with massive changes in diet and lifestyle. Interestingly, there was no evidence of any subsequent slowing down in mortality rates in any age group.

8.2.2 Socioeconomic differences in the rate of decline and shape of the trend: an emerging issue

In the UK, premature coronary heart disease death rates can be three to six times higher in the most deprived groups. They therefore remain a major contributor to social inequalities.

Furthermore, the flattening mortality rates for coronary heart disease among younger adults may represent an early warning sign. The decreasing absolute inequalities and the increase relative inequalities observed in age-adjusted rates suggest that deprivation has a significant role as a trend driver.

In Scotland, the observed flattening in the trends is apparently confined to the most deprived groups. As worse medical management of coronary heart disease in deprived young

adults appears implausible, unfavourable trends in the major risk factors for coronary heart disease, must provide the most likely explanation for these inequalities.

However, the lack of clear socio-economic gradient in the flattening in young adults in England represents an interesting contrast, and merits further consideration. Firstly, the risk factor trends in England have a complex socioeconomic patterning, and the net effect of these diverse risk factor trends might explain the discrepancy with Scotland. Secondly, the CHD modelling in England showed less marked social patterning of the contribution of risk factor changes among young adults. More detailed risk factor trend analyses using a modelling approach by socio-economic status are now urgently needed for Scotland, and for additional countries such as Australia and the Netherlands.

8.2.3 Results potentially explaining the trend drivers

Deaths from coronary heart disease in Poland have decreased rapidly after the great political, social and economic transformation commencing in 1989. This natural experiment offered a unique opportunity to examine the contributions of treatments and risk factors to the observed dramatic decline in mortality.

The major contributors to the Polish mortality fall were large changes in total cholesterol, plus beneficial trends in systolic blood pressure in women and decreased smoking in men. Physical activity also contributed. Together they explained about 55% of the observed mortality decline. Worryingly, adverse trends negated some of these benefits, specifically obesity, diabetes and blood pressure in men and smoking in women.

Evidence-based interventions explained about a third of the mortality fall in Poland. The most important treatment contributions came from therapies for heart failure, angina and secondary prevention. However, it is reasonable to assume that these benefits accrued over the 20 years period, while the abrupt change in diet and lifestyle was occurred within a very short period.

The rapid decline phase of the coronary heart disease epidemic in Poland is thus almost certainly attributable to changes in risk factors that can be linked to the major changes in

dietary factors as a consequence of the socio-political transition to a democracy and a market economy.

A modelling approach can also be used to try and help explained complex trends by socioeconomic status, by crudely quantifying the contribution of risk factors and treatments. In England, the $IMPACT_{sec}$ model suggests that approximately half the CHD mortality fall was attributable to improved treatment uptake. This benefit occurred evenly across all social groups, which reflects well on the UK National Health Service. Important gains were observed from falls in systolic blood pressure, probably reflecting population level policy interventions on salt. However, the contributions of other cardiovascular risk factors were smaller, reflecting modest recent decreases in powerful risk factors such as smoking and cholesterol. These benefits were then further eroded by continuing and substantial rises in obesity and diabetes prevalence.

8.2.4 Could the rapid changes in CHD mortality simply be artefacts?

These changes in coronary heart disease mortality could be due to artefacts. However, even brief reflection suggests that this appears very implausible. The flattening is consistently seen in similar age groups, has extended over many years or even a decade, and, crucially, has been observed in many countries.

Major changes in coding quality also appear implausible, as most of the countries where the flattening occurred have some of the best death certification systems in the world. The method use to correct rates in Poland was based on the trend observed in cardiovascular disease, usually a better quality level of coding, and similar to other approaches.[185] Differential coding precision by age is possible; however this generally tends to occur more frequently in older adults[341] , while the flattening has been observed mainly in younger adults.

It can also be postulated that a low rate might show an asymptotic pattern as it approaches a certain “minimum threshold”. Although theoretically possible, any such a threshold must be very low for coronary heart disease based on observations of event rates in individuals with very low overall cardiovascular risk.[135,136,342] A threshold based on cases exclusively based on genetically determined events is implausible, as most of the candidate genes and genome-wide association studies suggest that the gene-environment interaction is the main determinants of the expression of harmful phenotypes. [125] Moreover, the Scottish

data shows how rates in the same age-group by socio-economic status (and thus within a similar order of magnitude) might show different trend patterns.

A further key issue is that the trend analysis method used is sensitive to the length of the time periods considered. Therefore, phenomena happening at the end of the time series can be very dependent on the robustness of the rate. However, in the countries where flattening was observed, the period was sustained over several years. Australia and England are interesting cases in this regards, where the flattening was first identified based on a few years' observations and then persisted when the series were updated.

I have based my observations on the underlying determinants of the trends in Poland and England using a modelling approach. Many assumptions of the model are simplistic, and probably ignore potentially important determinants like life course influences or more complex trends over time. The models also failed to explain all the estimated deaths prevented or postponed. In part this can be attributed to the inherent uncertainty in the model parameters. Reassuringly, sensitivity analysis suggests that the main outputs of the models are not heavily influenced by imprecision. The effect of risk factors is probably underestimated because we assume that their effects are independent. On the other hand, the effect of treatments could be overestimated, particularly because we use effect measures based on randomized clinical trials. Treatment efficacy might be lower in the real world. However, the IMPACT model explicitly takes into account the uptake rates for treatments. Finally, some of the ages specific results are based on smaller numbers and thus, model outputs for age and gender specific analysis are correspondingly less robust.

In conclusion, the rapid changes in CHD mortality trends are therefore very unlikely to be artefacts. Although the role of evidence based treatments cannot be disregarded, the recent changes in mortality trends described in this thesis more plausibly mainly reflect changes in risk factors levels.

However, the conventional understanding of the development of CHD involves a long lag time, spanning decades. The rapid changes observed in recent CHD mortality trends therefore demand a better explanation.

In the following section, I will postulate some hypotheses in this respect.

8.3 MORTALITY RATES DYNAMISM – THREE HYPOTHESES

The rapid changes in mortality observed in the populations I have studied, can be the result of changes in the disease determinants. We do not know with certainty what is causing these changes. The causal framework for coronary heart disease is very well established. However, the temporal dynamics of these trends however does not fit very well into the accepted paradigm, so alternative explanations should perhaps be explored as competing hypotheses.

8.3.1 Do these dynamic changes reflect a reduction in CHD case fatality rates achieved by modern evidence-based treatments?

The explosion in evidence-based treatments for coronary heart disease impacting on mortality and morbidity started in the early 1980s. Furthermore, a few treatments were available earlier, such as coronary care units and medications for hypertension. They explain up to half the deaths prevented or postponed in many Western countries. They also have rapid effects, with most benefits achieved within a few months or years, and lasting over the longer term. However, such therapies cannot easily explain the sudden changes in mortality I have described.

In most Western countries, the decline in CHD mortality has been well underway following their peaks in the 1960s and the 1970s. Most of the "breakthrough" discoveries in coronary heart disease treatments were achieved in the late 1980s and 1990s (thrombolysis, angiotensin converting enzyme inhibitors, spironolactone in heart failure), although their wide adoption lagged considerably. Thus even in 2000, the uptake levels of evidence based treatments in health care systems in highly developed countries, like the US or the UK were remained unacceptably low[144,149], and substantial additional gains could be achieved by increasing their provision.[228 268]

The flattening in mortality in young adults US[192] and the similar patterns observed in England and Wales, Australia, the Netherlands and Scotland were essentially all starting during the last decade of the 20th century, when the evidence based treatment revolution was well underway. Thus, is implausible to consider that medical care in those settings subsequently deteriorated significantly.

In Poland, the abrupt decline in mortality cannot be solely attributed to a surge in evidence-based treatments. The trend was well underway in the first few years of the decline, continuing at the same pace over the period at the same time that the uptake of modern treatments increased from very low levels in 1991 to moderate levels in 2005.[252]

8.3.2 Are these dynamic changes the result of "triggers"?

As I described in chapter 3, triggers precipitate cardiovascular events by essentially harvesting from the high-risk pool in the population, generally detected as a "spike" in a longer trend. Shortly after that spike, the rate then briefly decreases to a subnormal low level, and then later recovers to its "endemic" level, usually over a period of days or weeks at most. This peak followed by a trough is sometimes termed the "harvesting" phenomenon.[127]

An individual might progressively accumulate atherosclerotic lesions and reach a period of vulnerability. Some of them will develop acute clinical events "triggered" by environmental factors acting in a short lag time scale, such as shovelling snow or peak pollution levels. If enough people in the population are in this period of vulnerability, sudden and rapid changes in the direction and speed of change might occur at the population level. In a declining trend, a "harvesting effect" – triggers causing events that would have otherwise happens a short period after exposure – might result in a slowing down or even a reversal of the declining trend for a period of time, and then the rate will catch up to its usual level .

The pattern of coronary heart disease mortality trends I described might be consistent with certain triggers like alcohol binge drinking pattern or cocaine abuse, both more prevalent in the young. However, the relative long period of time of sustained flattening is not consistent with the usual short time frame when triggers usually exert their effects. Trigger effects

associated with cardiovascular disease are usually seen within very short time scales (hours , days or weeks).[128] Furthermore, a recent study of myocardial infarction incidence and exposure to air pollution found evidence of a "harvesting effect".[343] In this time-series study, Bhaskaran et al observed an association between particulate air pollution exposure up to 6 hours after exposure but lack of association in longer time scales, measured in days. Influenza can increase the risk of cardiovascular events particularly among older people or people at high risk[344] and is generally considered a "trigger"[345]. However it follows a clear seasonal pattern with peaks in CVD admission rates lasting several weeks or months at most, and particularly noticeable in epidemic periods. In conclusion, the short-term nature of trigger effects completely fail to account for the long periods encompassing years of sluggish or no change in coronary heart disease mortality rates described earlier in this thesis.

Furthermore, any such trigger would need to demonstrate clear cohort effects or strong age specific effects, because the flattening of CHD mortality rates has been observed mainly in young adults. Cohort effects in coronary heart disease mortality trends seems to be rare, only reported in Singapore and Norway[116], thus cohort specific triggering events are likewise unlikely.

Age specific effects are more plausible. Binge drinking has been considered a trigger for cardiovascular events[128] , and is a common drinking pattern among the young.[346] However, its effects are only noticeable when rates are analysed over time periods measured in days or weeks [347,348] An interesting example is the midsummer celebrations in Finland, short term changes are observable following this alcohol excess , with a limited period of about three days of higher risk for cardiovascular events.[348] However, year on year cardiovascular disease mortality rates are decreasing in Finland.[349] Thus, although such triggering effects may be distinct, they cannot explain longer term Finnish trends. This peak of high mortality over a short time period thus fails to explain sustained periods of slow changing rates. The association of heavy alcohol intake has been implicated in rapid changes in mortality occurring over several years in the former soviet republics in adults[100], but this pattern and association has not been described in other settings, particularly the countries I have studied.

The association of very heavy alcohol intake and rapid changes in cardiovascular mortality within years has been reported in adults in the former Soviet republics.[100] However, this pattern has not been described in other settings, particularly the countries I have studied in this thesis.

Acute cocaine abuse has increased significantly among young cohorts, and is associated with acute cardiovascular morbidity and mortality.[350] However, most studies suggest a time window of some hours or one day at most.[128] Chronic cocaine abuse is associated with cardiovascular mortality and morbidity, but mainly associated with cardiomyopathy. Cocaine is also associated with smoking and chronic alcohol abuse[310] acting over a longer time scale. Chronic cocaine abuse is thus more a risk factor rather than a "triggering effect".

The trigger hypothesis singularly fails to explain the dramatic decline in mortality in those Central European countries joining the European Union after the collapse of the Soviet Union, where the rate of decline in CHD mortality was sustained over several years, without any evidence of subsequent "rebound".

Perhaps the most critical flaw in the triggering hypothesis is the very short time scale required, which is simply not consistent with longer periods of more sluggish rate change. The trend patterns which I have described in several countries lasted several years in a row. This suggests that the drivers of these sudden, rapid changes are attributable to determinants operating in a time scale of years, not months or days. Furthermore, they are probably acting on the forces that determine the size of both the high risk and low risk pools (affecting incidence or case fatality or both).

Because the causal paradigm for CHD has been extensively studied over the last six decades, a simpler explanation should take it fully into account.

8.3.3 Might risk factors operate over relatively short time scales? *Revising the classical CHD causal paradigm*

A key aspect of this causal paradigm is the lifelong time course of the disease extending over many decades.[12] Challenging this assumption and allowing shorter lag times for risk factor effects might explain the trend patterns in a simpler and more elegant way. There might also then be profound public health implications.

I have discussed in chapter 2 the basic disease mechanism of coronary heart disease. Most clinical features of the disease are caused by underlying atheroma, usually complicated by thrombosis which suddenly blocks a critical vessel. I have also discussed the evidence supporting an early life origin, with atheroma streaks developing in some teenagers and young adults, [3,4,351,352] and the substantial body of evidence to support the early developmental origins hypothesis.[113,115,353] This supports the notion that CHD and CVD have a long natural history extending over many decades or more probably over a lifetime.

Indeed, the traditional causal paradigm in the temporal relationship between risk factor changes and the corresponding changes in mortality previously favoured an "incubation period" lasting some decades. Geoffrey Rose suggested this was probably longer than 10 years[12], whereas Law et al proposed a lag time period of some three decades to explain the "French paradox", (whereby French CHD rates are much lower than UK rates in spite of similar current risk factor levels)[13]. The life course paradigm also lends support to the idea of long lag times in CHD.[353] And most extreme, Kelleher et al suggested that CVD trends in the mid 20th Century might reflect socioeconomic circumstance trends a century before.[354]

Reversibility of disease and reduction in risk has correspondingly been conventionally assumed to require decades. However, my results and other observations on the rapid changes in coronary heart disease mortality suggest that this paradigm needs urgent revision.

As I discussed previously, in the second half of the 20th century, most Western countries experienced sustained declines in age adjusted mortality rates, with consistent rates of decline over a period of several decades.[355]

However, the recent reversal of the decreasing trends in many countries in young adults I have described in this thesis (chapters 5 and 7) suggest that the hard won gains of the past could also be lost, and this could happen within a short time horizon.

Rates can also go up, like the rapid rise in CHD mortality rates in China in recent decades. I have also discussed examples of more complicated trends, like in Poland where after a period of steady rising, coronary heart disease mortality rates suddenly commenced a rapid decline in 1990 which continues today (chapter 6).

More rapid changes can also occur, when associated with major changes in environmental conditions. Thus, CHD mortality rates rose steadily during the 20th century and peaked in the 1970s and 1980s in the UK, Western Europe, and North America. However, close scrutiny of these national trends usually reveals a notch in the early 1940s. This disparity has been consistently attributed to sudden decreases in dietary intake of meat and animal fats because of rationing (as in the UK) or starvation (as in Holland and Norway) during World War II.[356]

This dynamism of CHD mortality rates clearly requires that the causation of coronary heart disease should also operate over shorter periods. Kuulusma et al analyzed data from the MONICA study and found that the association between risk factors and mortality rates improved if a lag time of just 3 to 4 years was taken into account.[224] Furthermore, data from randomized clinical trials of lipid or blood pressure reduction suggest that mortality reductions occur within the first few years of follow up.[24,357] Randomized Clinical Trials on diet[84] and dietary supplementation (GISSI PREVENZIONE)[358] likewise suggest that benefits are also observed within a very few years. Very short-term changes in CHD mortality have also been associated to particulate air exposure.[359] Equally important, rapid reductions in acute coronary events have been consistently observed within months of implementing smoke-free legislation in diverse countries. Thus, rapid reductions averaging 17% were recently reported following smoke free bans in Scotland and elsewhere.[360]

Numerous “natural experiments” also suggest that change can occur rapidly. I discussed the possible explanations for the abrupt decline in Poland following the break-up of the Soviet Union in 1989. Subsidies for meat and animal fats ended and consumption fell. This, plus substantial increases in vegetable oils and fresh fruit and vegetables quickly led to a 26%

decrease in CVD deaths between 1990 and 1994. These changes continued well into the 21st century, and the pace of decline keeps constant. Similar changes have been reported for Eastern Germany and the Czech Republic.[187,253] In this thesis, I showed that risk factors explained approximately 55% of the Polish decline in CHD mortality over the period, while evidence-based treatments only explained about a third. Furthermore, most of the treatment gains likely happened towards the end of the two decades period. Similar changes have been reported for Eastern Germany and the Czech Republic.[187,253]

Elsewhere, legislation in Mauritius during the 1990s, mandated polyunsaturated oils as a substitute for highly saturated cooking oils. Blood cholesterol levels fell 15% (0.8mmol/l) within five years.[361] Likewise, in Cuba, rapid CVD mortality falls followed a sharp and substantial reduction in calorie intake during the "special period" of the early 1990s.[362] In New Zealand, inequalities in life expectancy and CVD mortality have fluctuated in line with socio-economic changes. The lag time was consistently less than five years.[227] In Japan, successful salt reduction community based programs resulted in significant systolic blood pressure declines and 80% reduction in stroke mortality within a decade.[57] Even more rapid rises and falls in CVD mortality have recently been observed in Russia, partly reflecting the dramatic fluctuations in consumption of diverse forms of alcohol.[99]

Although there is an important body of evidence supporting the long period of atherosclerosis build up in the arterial system (See Chapter 3), the emergence of the vulnerable plaque paradigm and our increasing understanding of the role of thrombosis and inflammation might bring light to the often rapid time course of cardiovascular disease events.

Most acute coronary events happen in plaque that are less than 75% occlusive; this suggests that thrombosis and inflammation usually play a major role in both atherosclerosis build-up and also in precipitating acute events (by creating and exploiting vulnerable plaques).[2,363] The inflammatory and thrombotic milieu is a very dynamic environment. Changes can occur very rapidly (within minutes) and might in part explain the circadian variation in ACS occurrence.[364,365] Furthermore markers of inflammation like leptins or interleukin-6 have been also associated on the long term (years) with CHD events, even taken into account short-term individual variation.[366,367]

Since the different pathologic processes leading to plaque development, instability rupture and occlusion act on different time scales, subsequent clinical events might reasonably be considered to reflect the complex interplay of causal risk factors acting on different time scales.

Dietary and lifestyle risk factors can be linked to inflammatory and thrombotic mechanisms in the atherosclerotic plaque. There are strong links between metabolism and inflammation and thrombosis. [363] For example, the effects on inflammation markers may explain the enormous risk associated with transfat consumption[368], or the increased production of pro-inflammatory adipokines observed in patients with central obesity or diabetes.[369] Furthermore, lifestyle factors like smoking[370] and physical activity[371] have been associated with specific thrombotic and inflammatory processes operating at plaque level.

Diet and lifestyle are thus not only determinants of the classical risk factors, involved in the long term build up atheroma, but also might be associated with biological and thrombotic events happening over much shorter time scales. The recent flattening in mortality observed in some Western countries and the natural experiments observed in Finland, Eastern Europe, Cuba and Mauritius provide population level observations compatible with this hypothesis.

8.4 PUBLIC HEALTH POLICY IMPLICATIONS OF RAPID CHANGES IN CHD MORTALITY RATES

The rapid response of mortality trends to changes in risk factors, acting at the population level provides further support to the importance of preventative strategies to decrease the future cardiovascular burden.

A pro-active public health approach also makes strong scientific economic sense. Such measures might include increased tobacco controls, improving the contents of food products (re-formulation); controls on the marketing of energy dense, nutrient poor, high fat, salt and sugar processed foods; package labelling, taxation of junk food and subsidies for healthier foods. Making commercial markets more health promoting and boosting the affordability of healthier diet options could be substantially cost saving. [372] [373]

These types of policies are difficult to evaluate with traditional research methods, and we may therefore gain insights on the potential benefits by using a modelling approach. For example, in the UK, the National Institute for Clinical Excellence (NICE) recently commissioned detailed economic modelling. A spreadsheet model was developed which generated a relative risk of primary CVD across the entire England and Wales population of 50 million for each successive year. In brief, reducing mean population cholesterol or blood pressure levels by 5% could result in discounted annual savings of approximately £0.7 billion and £0.9 billion respectively.[328]

Reducing population cardiovascular risk by even one percent might generate discounted savings of approximately £260millions per year. [328] Additional benefits to existing CVD patients, and the inevitable reductions in other diseases were not quantified. However, halving CVD events across the entire population might result in discounted savings of approximately £14 billion per year.[328]

As with any modelling exercise, ranges of usually conservative assumptions are made, with the general result of probably underestimate the true gains. For example, usually benefits are discounted, because in general future gains are valued at a lower level than present or short-term gains. An important implication for estimating future disease burden is that If lag

times operates over a time horizon of years instead of decades, these benefits are greater, since discounting will be smaller.

Of course, policy-based prevention strategies are challenging and many politicians would instead prefer to rely on voluntary agreements with industry or focus on individual responsibility. Moreover, if preventative strategies are expected to work only in the long term, urgent issues might compete for scarce resources, reducing the value of these policies for real world policy decision making. Policy makers thus need to overcome their natural reluctance to legislate mandatory action. This becomes easier when the situation urgently demands it, for example, when the pace of change in mortality rates is not sufficient or when the "epidemic" of childhood obesity continues to increase, in spite of numerous well meaning but ineffective initiatives.[329]

The accumulating evidence in my thesis that change in a hard outcome like population CHD mortality can occur rapidly after intervening on cardiovascular risk factors could also help when prioritizing different policy options. However, the timescales of policy maker's decisions are usually short term. In the UK for example, the need to demonstrate impact within the 4 year political cycle and the requirement to 'balance the books' within the annual commissioning cycle[374], makes it difficult for planners to prioritise prevention when assuming the "long time scale paradigm". However, the rapid changes I have described in this thesis may help them to remove such perceived but false barriers, and instead consider more radical interventions.

Action is urgently required, because the global burden of non communicable diseases is rapidly increasing, as I discussed earlier. The control of the CHD epidemic across communities and populations is not immune to "adoption delays". The earlier start of the decline phase in the US started at the beginning of the 60s in California, Maryland and the District of Columbia but in the southeast states only started five years later.[193] Globally, Western countries started in the 1970s-1980s, while most middle income and low income countries still experiencing the rapid increase phase of their cardiovascular epidemics.

In 2011, the first UN High level summit on the prevention and control of Non Communicable disease was held, looking to engage member countries in a concerted and

accountable effort to tackle one of the key challenges of the upcoming decades. Time will tell if this will be translated in decisive action.

Our knowledge of what we need to do is thus already substantial, the proof of its efficacy is considerable, and the examples of the early adopters are now more widely known. More effort should therefore be directed to increase the adoption of effective strategies by more communities.[177]

In conclusion, population wide interventions aimed at the major diet and lifestyle determinants of cardiovascular disease can have large benefits. Furthermore, this could happen quickly, within a few years. This also makes strong economic and political sense. It seems that prevention of cardiovascular diseases could score big, and also fast, even within the electoral term of many politicians and policymakers.

8.5 FURTHER RESEARCH

Linking trends in CHD mortality with trends in risk factors remains a research priority. Such studies are not easy to perform, as they traditionally require following large cohorts over years or decades. Furthermore, these studies often have issues related to generalisability.

In contrast, modelling studies potentially offer the opportunity to study many of the trends in contexts that are more relevant for policy makers. To some extent, IMPACT and other CHD models have addressed this, but mainly for simple linear trends. More sophisticated modelling approaches are now indicated to explore complex multi-dimensional trends in mortality and risk factors for CVD, and for wider non-communicable diseases.

Studies that provide population answers will ultimately have to rely on long time series of risk factors and mortality in representative samples. However, such data are not easily available for most populations. An important recent development in this regard is the methodology developed by the latest version of the Global Burden of Disease study, currently underway. They implemented a multilevel hierarchical approach to estimate risk factors trends for settings with few data sources.[64,138,139,141] This type of data can be used in trend analysis studies within a multivariate, time-series regression framework like ARIMA. These methods allow the use of covariates and could be helpful in studying and explaining the ongoing disease trends.

The England and Wales analyses described earlier demonstrated mortality flattening without significant differences across socioeconomic levels. This may be partly explained by the complex pattern of risk factors trends in socio economic groups. The hypothesis that the mortality trends differentials can be attributed to risk factor trends differential is therefore not yet proved nor disproved. The effect of risk factors on mortality (as a proxy for incidence) is complex, and the net effects might depend in many other factors including baseline risk and changes in population structure over time. Alternatively, the socio-economic measures currently available may simply be inadequate to highlight socioeconomic differences in both mortality trends and risk factors trends. We have extended the IMPACT model to analyze trends by socioeconomic status, and performing analysis on England and Scotland, to further explore the relationship between socioeconomic differentials and trend drivers in CHD mortality. This approach may in future allow us to explore whether the observed mortality flattening in

Scotland which shows marked inequalities by socioeconomic status, is related to risk factor trends differential by a measure of deprivation.

One of the issues limiting the approach I used to identify points in time where a trend showed a different pace of change is the "sensitivity" of mortality rates to change in the number of events, particularly when rates are low, and thus less robust. Although Joinpoint regression models provide ways of controlling the numbers of years that will be considered into estimates of periods of constant change, a trend based on few years could be still heavily dependent by unstable rates at the end of the period. The way the trend analysis methods find out change points in the trend thus becomes important. Recently, Martinez-Beneito[375] proposed a Bayesian approach to Joinpoint inference, that could to some extent address this issue. The originality of this approach is that it is possible to propose a "prior model" and then use the data to estimate a "posterior model". In that sense, more flexibility for model selection can be achieved, instead of considering as the baseline comparison a model with no joinpoint (a linear trend).

Other time series methods employ cumulative change. These are generally known as Change point methods; an example of these is the CUSUM approach using in statistical process control methods. They can offer some insights, but are usually more useful for applications involving continuous variables.

Simulation modelling approaches could also help our approach to sensitivity analysis. Incidence models that synthesize data on population, risk factors trends and case fatality can be developed for this purposes, and explore different assumptions in terms of mortality trend's shape, pace of change and absolute or relative changes. Such models can also be extended to integrate information on long time series of CHD determinants acting on different time scales: life courses influences, biological established risk factors, and triggers. We are therefore now developing a policy model called IMPACT2 as a generic modelling platform that could in future perhaps be used for this purpose. [376]

8.6 LESSONS I HAVE LEARNED DURING THIS PHD WORK

Time is a complex variable in every epidemiological analysis. The time dimension of the CHD epidemic is particularly challenging. Useful insights are difficult to obtain with informal, descriptive analyses or simple, age-adjusted analysis. I therefore needed to identify and use more appropriate study methods, like time-series analysis techniques. Nevertheless, because time is important, continuing monitoring of rates is crucial to make sense of ongoing trend changes.

The analysis of mortality rates is frequently seen as a limited exercise particularly when done in a simplistic way. Even more, they are often overlooked altogether, or used as "off the shelf" paragraphs to justify importance or relevance of the study. However, they remain an essential part of the epidemiologist's work, and the recent changes in CHD trends and the challenges they pose to central tenets of the coronary heart disease causation paradigm can be exciting.

I enjoyed explaining an unusual method (Joinpoint) to reviewers during the peer review process of my papers, and when helping colleagues wishing to analyse their own data. This experience showed me the vital importance of clear and succinct communication of complex issues, without simply referring to other work, or resorting to technical language. The general reader should be helped to clearly understand the essential features of the particular technique being used, in order to enable them to critically appraise your work.

Finally, hypothesis generating analyses are potentially important studies, even though mainstream peer-reviewed epidemiological research may look at them with some suspicion. They do not have the solidity of hypothesis-testing studies and might understandably go unnoticed. However, when the hypothesis is focused on important policy issues and explicitly addresses the implications for prevention and public health, editors, reviewers and readers may often welcome this type of analysis.

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10 APPENDICES

A1. Example of model selection with the Joinpoint regression technique. England & Wales coronary heart mortality trends

Both the Permutation test method and the Bayesian Information criterion method (BIC) try to find the simplest trend that fits the data well. The simplest case is therefore the model with no joinpoints, e.g., a linear trend. The BIC approach finds the model with the best fit by penalizing the cost of extra parameters (e.g. more joinpoints) , although fitting well the data, they are less parsimonious . The k-joinpoint model with the minimum value of BIC(k) is selected as the final model.

The permutation test approach test if the alternative hypothesis of a trend with more joinpoints can be accepted instead of the null hypothesis of a trend with fewer joinpoints, adjusting for multiple comparisons.

For example, for men aged 35-44 the best model is the one with 2 joinpoints, with a BIC of -13.98 (see table A1-1). The permutation test approach finds as well that the best model consist of 2 joinpoints, with a probability of type I error <0.01 , adjusted for multiple comparisons.

A comparison of both approaches is presented in tables A1-1 and A1-2.

Table A1-1 Model selection using a Bayesian Information Criterion (BIC) approach. Men, England & Wales

Age [years]	Bayesian Information criterion							Permutation tests						
	Model	JP	n	P	df	Σ SE	BIC	Test	JP, H0	JP, H1	N, df	D, df	Permu-tations	P**
35-44	#1	0	21	2	19	1.7E-05	-13.7	#1	0*	3	6	13	4500	0.026
	#2	1	21	4	17	1.2E-05	-13.8	#2	0	2 *	4	15	4500	0.010
	#3	2	21	6	15	7.4E-06	-14.0	#3	1	2*	2	15	4500	0.020
	#4	*3*	*21*	*8*		7.5E-06	-13.7							
	Final Selected Model 2 Joinpoint(s)							*Final Selected Model 2 Joinpoint(s)*						
45-54	#1	0	21	2	19	1.6E-04	-11.5							
	#2	1	21	4	17	4.7E-05	-12.4	#1	0	3*	6	13	4500	0.000
	#3	2	21	6	15	1.6E-05	-13.2	#2	1	3*	4	13	4500	0.000
	#4	3	21	8	13	9.8E-06	-13.4	#3	2	3*	2	13	4500	0.024
	Final Selected Model 3 Joinpoint(s)							*Final Selected Model 3 Joinpoint(s)*						
55-64	#1	0	21	2	19	5.0E-04	-10.4	#1	0	3*	6	13	4500	0.000
	#2	1	21	4	17	6.7E-05	-12.1	#2	1	3*	4	13	4500	0.000
	#3	2	21	6	15	2.2E-05	-12.9	#3	2	3*	2	13	4500	0.012
	#4	3	21	8	13	1.1E-05	-13.3							
	Final Selected Model 3 Joinpoint(s)							*Final Selected Model 3 Joinpoint(s)*						
65-74	#1	0	21	2	19	5.2E-04	-10.3	#1	0	3*	6	13	4500	0.000
	#2	1	21	4	17	6.0E-05	-12.2	#2	1	3*	4	13	4500	0.010
	#3	2	21	6	15	3.4E-05	-12.5	#3	2*	3	2	13	4500	0.083
	#4	3	21	8	13	2.7E-05	-12.4							
	Final Selected Model 2 Joinpoint(s)							*Final Selected Model 2 Joinpoint(s)*						
75+	#1	0	21	2	19	1.8E-03	-9.1	#1	0	3*	6	13	4500	0.000
	#2	1	21	4	17	5.1E-04	-10.0	#2	1	3*	4	13	4500	0.001
	#3	2	21	6	15	1.9E-04	-10.7	#3	2*	3	2	13	4500	0.778
	#4	3	21	8	13	1.8E-04	-10.5							
	Final Selected Model 2 Joinpoint(s)							Final Selected Model 2 Joinpoint(s)						

BIC: Bayesian Information Criterion df:degrees of freedom JP: joinpoints n: number of observations P: number of parameters Σ SE: sum of squared errors
N, df: numerator degrees of freedom D,df:Denominator degrees of freedom ** p : p value with multiple comparisons adjustment (Bonferroni)

Table A1-2 Model selection using a Bayesian Information Criterion (BIC) approach. Women, England & Wales

Age [years]	Bayesian Information criterion							Permutation tests						
	Model	JP	n	P	df	Σ SE	BIC	Test	JP, H0	JP, H1	N, df	D, df	Permu-tations	P**
35-44	#1	0	21	2	19	1.7E-06	-15.7	#1	0*	3	6	13	4500	0.294
	#2	1	21	4	17	2.1E-06	-15.5	#2	0*	2	4	15	4500	0.307
	#3	2	21	6	15	1.8E-06	-15.4	#3	0*	1	2	17	4500	0.367
	#4	3	21	8	13	1.6E-06	-15.2							
			Final Selected Model 2 Joinpoint(s)							*Final Selected Model 2 Joinpoint(s)*				
45-54		0	21	2	19	2.3E-05	-13.4	#1	0	3*	6	13	4500	0.000
		1	21	4	17	5.8E-06	-14.5	#2	1*	3	4	13	4500	0.103
		2	21	6	15	4.2E-06	-14.6	#3	1*	2	2	13	4500	0.098
		3	21	8	13	3.7E-06	-14.4							
			Final Selected Model 3 Joinpoint(s)							*Final Selected Model 3 Joinpoint(s)*				
55-64		0	21	2	19	3.2E-04	-10.8	#1	0	3*	6	13	4500	0.000
		1	21	4	17	4.7E-05	-12.4	#2	1	3*	4	13	4500	0.000
		2	21	6	15	1.2E-05	-13.5	#3	2*	3	2	13	4500	0.086
		3	21	8	13	9.2E-05	-13.5							
			Final Selected Model 3 Joinpoint(s)							*Final Selected Model 3 Joinpoint(s)*				
65-74		0	21	2	19	3.2E-04	-10.8	#1	0	3*	6	13	4500	0.000
		1	21	4	17	3.6E-05	-12.7	#2	1	3*	4	13	4500	0.001
		2	21	6	15	1.4E-05	-13.3	#3	2*	3	2	13	4500	0.469
		3	21	8	13	1.3E-05	-13.1							
			Final Selected Model 2 Joinpoint(s)							*Final Selected Model 2 Joinpoint(s)*				
75+		0	21	2	19	6.5E-04	-10.1	#1	0	3*	6	13	4500	0.000
		1	21	4	17	2.5E-04	-10.8	#2	1	3*	4	13	4500	0.008
		2	21	6	15	1.9E-05	-10.7	#3	2	3*	2	13	4500	0.013
		3	21	8	13	1.2E-05	-10.9							
			Final Selected Model 2 Joinpoint(s)							Final Selected Model 2 Joinpoint(s)				

BIC: Bayesian Information Criterion df:degrees of freedom JP: joinpoints n: number of observations P: number of parameters Σ SE: sum of squared errors
N, df: numerator degrees of freedom D,df:Denominator degrees of freedom * hypothesis accepted ** p : p value with multiple comparisons adjustment (Bonferroni)

A2. The Polish IMPACT Model: Methods and data sources

IMPACT is a deterministic, cell-based policy model. It uses epidemiological information to estimate the contributions of population-level risk factor changes (impacting mainly on incidence) and changes in the uptake of evidence-based treatments (impacting mainly on case fatality) between two points in time (the start-year and the end-year). The primary outcome measure of the model is the deaths prevented or postponed (DPPs).

The starting point for the model is to calculate the 'target' number of deaths the model needs to explain. This target number is obtained by using death counts recorded in the official registration system to calculate the difference between the actual observed Coronary Heart Disease (CHD) deaths recorded in the end-year from expected deaths, i.e. the number that would have occurred in the end-year had the CHD mortality rates remained the same as in the start-year.

The calculation of the modelled estimate of DPPs rests on utilising two well-studied relationships: firstly, that between risk factor change and the relative reduction in CHD mortality; secondly, that between treatment uptake and reductions in case-fatality in patients with a specific form of CHD.

The model applies the relative risk reduction quantified in previous randomised controlled trials and meta-analyses to estimate the mortality reduction attributable to: a) temporal change in risk factor prevalence (in those without diagnosed CHD) to calculate the DPPs 'explained' by specific risk factor trends; b) net change over the period in the uptake of specific treatments in patients with each specific form of CHD to estimate DPPs 'explained' owing to improved 1-year case fatality rates. Great care is taken to avoid double counting the same individuals.

The mortality benefits from risk factor changes in the population, and treatment benefits in patient groups are then summed. This sum represents the DPPs 'explained' by the model.

At the end of the modelling process, the total DPPs 'explained' by the model is then compared with the observed fall in deaths (the 'target' to be explained). Model fit is therefore calculated as the difference between the observed deaths and model DPPs, and expressed as the percentage explained. This measures the extent to which the model was successful in explaining the observed change in the CHD mortality in the population.

A policy model like IMPACT stands in contrast to a typical multivariate regression model because it seeks to synthesise best estimates from a variety of sources to reliably estimate the extent to which a range of factors, acting in combination, explain or predict an outcome. We did not obtain the parameters for this model by running regressions. Rather, the model incorporates the best coefficients from the largest meta-analysis or randomised controlled trials of the reduction in case fatality attributed to treatment or the independent effect sizes of a unit change in each risk factor on CHD mortality.

The tables included in this appendix document provide details about the methods that were used in creating the Polish IMPACT model. This model examines the effects of changes in treatments and risk factors trends on changes in mortality from coronary heart disease (CHD) among Polish adults aged 25-74 years. Earlier versions of the IMPACT mortality model have been previously applied to data from Europe, USA, New Zealand and China.[1-7] This cell-based mortality model, developed in Microsoft Excel, has been described in detail online and elsewhere[3-4]

***A2-1 Expected* and *observed* number of deaths from CHD**

The data sources needed to estimate the expected and observed numbers of deaths from CHD for 2005 are shown in Table A2-2. The expected number of deaths from CHD in 2005 was calculated by multiplying the age-specific mortality rates from CHD in 1991 by the population counts for 2005 in that age-stratum. Summing over all age strata then yielded the *expected* numbers of deaths from CHD. The difference between the number of *expected* and *observed* number of deaths from CHD represents the mortality fall, the total number of *deaths prevented or postponed* (**DPPs**) from the combined changes in treatment patterns and risk factor prevalence.

A2-2 Treatments in the Polish IMPACT Model.

The treatment arm of the Model includes the following populations of patients:

- those hospitalized with an acute myocardial infarction (AMI),
- patients admitted to the hospital with unstable angina,
- community-dwelling patients who have survived an AMI,
- patients who have undergone revascularization procedure (coronary artery bypass grafting (CABG), or a percutaneous coronary intervention (PCI), with or without stent.
- community-dwelling patients with angina pectoris (no revascularization)
- patients admitted to hospital with heart failure,
- community-dwelling patients with heart failure (no hospital admission).
- Hypertensive individuals eligible for hypotensive therapy
- Hypercholesterolaemic subjects eligible for cholesterol lowering therapy

The main data sources used to estimate the numbers of these groups are shown in Table A2-2. For each of the groups, we estimated the number of DPPs that were attributable to various treatments. A listing of the treatments that were considered in the model and the data sources used to estimate the percentages of patients receiving treatments are shown in Tables A2-3 and A2-4.

The general approach to calculating the number of DPPs from an intervention among a particular patient group was first to stratify by age and sex, then to multiply the estimated number of patients in the year 2005 by the proportion of these patients receiving a particular treatment, by the 1-year case-fatality rate, and by the relative reduction in the case-fatality rate due to the administered treatment. Sources for estimates of efficacy (relative risk reductions) are shown in Table A2-3. Sources for treatment uptakes are shown in Table A2- 4.

Age-specific case-fatality rates for each patient group are presented in Table A2-5.

We assumed that compliance (concordance)**,** the proportion of treated patients actually taking therapeutically effective levels of medication, was 100% among hospital patients, 70% among symptomatic community patients, and 50% among asymptomatic community patients[8-9]

All these assumptions were tested in subsequent sensitivity analyses.

EXAMPLE 1: estimation of DPPs from a specific treatment

For example, in Poland, in 2005, approximately 12 230 men aged 55-64 were hospitalized with acute myocardial infarction (AMI). The expected age-specific 1-year case-fatality rate without treatment for this group was approximately 5.4%. From registry data[10] 96% of them were given aspirin or other antiplatelet drug, interventions with an expected mortality reduction of 15%. the number of deaths prevented or postponed for at least a year by the use of aspirin among men aged 55 to 64 were then calculated as:

[Eq1] 12 230 x 0.054 x 0.96 x 0.15 = 95

This calculation was then repeated

a) for men and women in each age group, and

b) incorporating a Mant and Hicks adjustment for multiple medications

c) using maximum and minimum values for each parameter in each group, to generate a sensitivity analysis (see below).

A2-3 Risk factors in the Polish IMPACT model

The second part of the IMPACT model involves estimating the number of coronary heart disease DPPs related to changes in cardiovascular risk factor levels in the population. The Polish IMPACT model includes smoking, total cholesterol, systolic blood pressure, body mass index, diabetes, and physical activity. Data sources used to calculate the trends in the prevalence (or mean values) of the specific risk factors are shown in Table A2-2.

Two approaches to calculating DPPs from changes in risk factors were used.

In the **Regression approach**—used for systolic blood pressure, total cholesterol, and body mass index--the number of deaths from CHD occurring in 1991 (the base year) were multiplied by the absolute change in risk factor prevalence, and by a regression coefficient quantifying the change in CHD mortality that would result from the change in risk factor level. Natural logarithms were used, as is conventional, in order to best describe the log-linear relationship between changes in risk factor levels and mortality.

In the **Population attributable risk fraction approach**, the reduction in deaths attributable to change in a risk factor level is calculated based on the change in the attributable risk fraction for that risk factor between the initial and final year of the model.

EXAMPLE 2: estimation of DPPs from risk factor change using regression method:

Mortality fall due to reduction in systolic blood pressure in women aged 55-64

For example, in 1991, there were 2534 CHD deaths among women aged 55-64 years. Mean systolic blood pressure in this group decreased by 5.4 mmHg between 1991 and 2005. The meta-analysis reports an estimated age- and sex-specific reduction in mortality of 50 percent for every 20 mmHg reduction in systolic blood pressure, generating a logarithmic coefficient of –0.035. [11] The number of deaths prevented or postponed was then estimated as:

[Eq2] [deaths in 1991] * (1-EXP(coefficient*change)

= 2534 (1-EXP(-0.035*5.4)) = 436

This calculation was then repeated

a) for men and women in each age group, and

b) using maximum and minimum values in each group, to generate a sensitivity analysis.

Data sources for the number of CHD deaths are shown in Table A2-2, sources for the population means of risk factors are shown in Table A2-2, and sources for the coefficients used in these analyses are listed in Table A2-6.

EXAMPLE 3: estimation of DPPs from risk factor change using PARF method

The **population-attributable risk factor (PARF) approach** was used for smoking, diabetes, and physical activity. PARF was calculated conventionally as

(P x (RR-1)) / (1+P x (RR-1))

where P - prevalence of the risk factor and RR - the relative risk for CHD mortality associated with that risk factor. To assess the decline in CHD mortality the number of coronary heart disease deaths in 1991 (the base year) was multiplied by the difference between the population-attributable risk fraction in 1991 and that in 2005.

For example, the prevalence of diabetes among women aged 65-74 years was 8.7% in 1991 and 12.9% in 2005. Assuming a Relative Risk of 2.59[12], the PARF was ~0.1215 in 1991 and ~0.1702 in 2005. Assuming the number of CHD deaths in 1991 = 7,180, The number of deaths attributable to the increase in diabetes prevalence from 1991 to 2005 was therefore

(7 180) * (0.170 - 0.122) = ~350 DPPs

This calculation was then repeated

a) for men and women in each age group,b) for physical inactivity and smoking

c) using maximum and minimum values in each group, to generate a sensitivity analysis

Data sources for the prevalence of risk factors and for the number of CHD deaths are shown in Table 2. Sources for the relative risks used in these PARF analyses are listed in Table 7. All come from the InterHeart study[12], the largest international study to provide *independent* RR values, adjusted for other major risk factors.

The rationale for choosing the regression or PARF approaches for specific risk factors in the Polish IMPACT Model is detailed in Table A2-8.

A2-4 Other Methodological Considerations

Several methodological issues will be discussed below. These include adjusting the relative reduction in case-fatality rate for patients receiving multiple treatments, establishing rules for avoiding double-counting individual patients who may fall into more than a single disease category (patient group), treatment overlaps, and sensitivity analyses.

Polypharmacy Issues

Individual CHD patients may take a number of different medications. However, data from randomized clinical trials on efficacy of treatment combinations are sparse. Mant and Hicks suggested a method to estimate case-fatality reduction by polypharmacy[13]. This approach was subsequently endorsed by Yusuf[14] and Law and Wald[15].

EXAMPLE 4: estimation of reduced benefit if patient taking multiple medications (Mant and Hicks approach)

If we take the example **of secondary prevention following acute myocardial infarction,** good evidence (Table A2-3) suggests that, for each intervention, the relative reduction in case fatality is approximately: aspirin 15%, beta-blockers 23%, ACE inhibitors 20%, statins 22% and rehabilitation 26%. The Mant and Hicks approach suggests that in individual patients receiving all these interventions, case-fatality reduction is very unlikely to be simply additive, i.e. not **106%** (15% + 23%+ 20% + 22% + 26%). Instead, having considered the 15% case fatality reduction achieved by aspirin, the next medication, in this case a beta-blocker, can only reduce the **residual** case fatality (1-15%). Likewise, the subsequent addition of an ACE inhibitor can then only decrease the **remaining** case fatality, which will be 1 - [(1- 0.15) X (1-0.23)].

The **Mant and Hicks approach** therefore suggests that a **cumulative relative benefit** can be estimated as follows:

Relative Benefit = 1 - [(1-relative reduction in case-fatality rate for treatment A) X (1- relative reduction in case-fatality rate for treatment B) X ...X (1- relative reduction in case-fatality rate for treatment N).

In considering appropriate treatments for AMI survivors, applying relative risk reductions (RRR) for aspirin, beta-blockers ACE inhibitors statins and rehabilitation then gives:

Relative Benefit = 1 - [(1 –aspirin RRR) X (1 - beta-blockers RRR) X (1 - ACE inhibitors RRR) X (1- statins RRR) X (1- rehabilitation RRR)]

= 1 - [(1- 0.15) X (1-0.23) X (1-0.20) X (1- 0.22) X (1- 0.26)]

= 1 - [(0.85) X (0.77) X (0.80) X (0.78) X (0.74)]

= **0.70 i.e. a 70% lower case fatality**

This represents a **34%** relative reduction (0.70/1.06) on the simple additive value of **106%.**

Potential overlaps between patient groups: avoiding double counting

There are potential overlaps between CHD patient groups (Table A2-9).

For example, approximately half the patients having CABG surgery have a previous AMI[16], approximately 25% of AMI survivors develop heart failure within 12 months[17], and over 50% of CHD patients have a history of hypertension[18]. All these assumptions were tested in subsequent sensitivity analyses.

Sensitivity Analyses

Because of uncertainties surrounding many of the values, a multi-way sensitivity analysis was performed using the analysis of extremes method[19]. For each model parameter, a lower and upper value was assigned using either 95% confidence intervals where available (for instance therapeutic effectiveness quantified as a relative risk reduction in the relevant meta-analyses), or otherwise plus or minus 20%.

An analysis of extremes was therefore performed whereby the maximum and minimum feasible values were fed in to the model. By multiplying through, the resulting product then generated maximum and minimum estimates for deaths prevented or postponed (Table A2-1).

EXAMPLE: sensitivity analysis for AMI patients given aspirin

An example of calculating lower and upper-bound estimates for DPPs for treatment with aspirin among men aged 55-64 years who were hospitalized with an AMI is presented here. 95% confidence intervals from the meta-analysis were used for relative mortality reduction; lower and upper bound estimates for the other parameters were calculated as minus or plus 20% [except for treatment uptake that was capped at 99%]. Multiplying all the lower-bound estimates yielded the minimum [lower bound] estimate and multiplying the upper-bound estimates yielded the maximum [upper bound] estimate.

Table A2-1 Example of sensitivity analysis

	Patient numbers	Treatment Uptake	Relative mortality reduction*	One year case fatality	Deaths prevented or postponed
	A	B	C	D	(A x B x C x D)
Best Estimate	12 226	0.96	0.15	0.054	95
Minimum estimate	9 781	0.77	11%*	0.043	36
Maximum estimate	14671	0.99	19%*	0.065	179

* 95% CI from the Antithrombotic Trialists' Collaboration meta-analysis[20], see Table A2-3.

A2-5 Sources of data used in Polish IMPACT Model

Table A2-2. Main Data Sources for the Parameters Used in the Polish IMPACT Model

Item	1991	2005
Population statistics (number)	Central Statistical Office	Central Statistical Office
Deaths by age and sex (number)	NIPH (ICD-9 codes 410-414)*	NIPH (ICD-10 codes I20-25)
Number of patients admitted yearly		
Myocardial infarction: ICD9:	NIPH	NIPH
Angina pectoris: ICD9: 413	NIPH	NIPH
Heart failure: ICD10: I50	NIPH	NIPH
Number of patients treated		
CABG	KROK	KROK
PCI	Assume zero	PL-ACS
Cardiopulmonary resuscitation in the community		
Numbers & Uptake		
Uptake	Assume 1% of admitted AMI patients	Rudner et al[21]
Acute myocardial infarction		
Hospital Resuscitation	Assume 2% of admitted AMI	PL-ACS, NIPH
Thrombolysis	MONICA	PL-ACS, NIPH
Primary angioplasty	Assume zero	PL-ACS, NIPH
Aspirin	MONICA	PL-ACS, NIPH

Table A2-2 (Continued)

Item	1991	2005
Beta blockers	MONICA	PL-ACS, NIPH
ACE inhibitors	MONICA	PL-ACS, NIPH
Primary CABG surgery	Assume zero	PL-ACS, NIPH
Primary PCI (angioplasty)	Assume zero	PL-ACS, NIPH
Angina pectoris: unstable		
Prevalence	Extrapolated	NIPH
Platelet IIB/IIIA Inhibitors	Assume zero	PL-ACS
Aspirin alone	Expert opinion	PL-ACS
Aspirin & Heparin	Expert opinion	PL-ACS
Primary CABG surgery	Assume zero	PL-ACS, KROK
Primary PCI (angioplasty)	Assume zero	PL-ACS
Aspirin	Pol-MONICA	WOBASZ, SPOK
Beta blockers	Pol-MONICA	WOBASZ, SPOK
ACE inhibitors	Assume zero	WOBASZ, SPOK
Statins	Assume zero	WOBASZ, SPOK
Warfarin	Assume zero	WOBASZ
Secondary prevention following CABG or PCI		
Aspirin	Assume zero	WOBASZ
Beta blockers	Assume zero	WOBASZ
ACE inhibitors	Assume zero	WOBASZ
Statins	Assume zero	WOBASZ
Warfarin	Assume zero	WOBASZ
Rehabilitation	Assume zero	EUROASPIRE
Congestive Heart Failure		
ACE inhibitors	Assume zero	HF2005
Beta blockers	Assume zero	HF2005
Spironolactone	Assume zero	HF2005
Aspirin	Assume zero	HF2005
Statins	Assume zero	HF2005
Treatment for chronic angina		
CABG surgery	KROK	NHDS
PCI (angioplasty)	Assume zero	NHDS
Community angina pectoris: total		
Prevalence		WOBASZ
Aspirin	Assume zero	WOBASZ
Statins	Assume zero	WOBASZ
Community Chronic heart failure		
Prevalence		Expert opinion, Spanish data
ACE inhibitors	Assume zero	HF2005
Beta blockers	Assume zero	HF2005
Spironolactone	Assume zero	HF2005
Aspirin	Assume zero	HF2005

Table A2-2 (Continued)

Item	1991	2005
Statins	Assume zero	HF2005
Hypertension		
Prevalence	NATPOL II (1996)	WOBASZ
Treated (%)	NATPOL II (1996)	WOBASZ
Statins etc for primary prevention		
Hypercholesterolemia (%)	not needed	WOBASZ
Treated (%)	Assume zero	WOBASZ
Population RISK FACTOR prevalence		
Current smoking	Central Statistical Office	Central Statistical Office
Systolic blood pressure	NATPOL 1997 (extrapolated to 1991)	WOBASZ
Cholesterol	MONICA	MONICA
Physical activity	NATPOL 1997 (extrapolated to 1991)	WOBASZ
Obesity (BMI)	NATPOL 1997 (extrapolated to 1991)	WOBASZ
Diabetes	NATPOL 1997 (extrapolated to 1991)	WOBASZ

*corrected for change in death registry system[22]

Key:

ACE denotes angiotensin-converting enzyme, AMI acute myocardial infarction, CABG coronary artery bypass graft surgery, GUS – Central Statistical Office, HF2005 – Multicenter Study of Heart Failure Treatment in Poland (2005), ICD International Classification of Diseases, KROK – Cardiosurgery Registry, NATPOL – set of country representative cardiovascular risk factors surveys, NIPH – National Institute of Public Health, PL-ACS Polish Acute Coronary Syndromes Registry, PCI percutaneous coronary intervention, WOBASZ – Multicenter Study on Health of Polish Citizens.

Table A2-2. Clinical efficacy of interventions: relative risk reductions obtained from meta-analyses, and randomised controlled trials*

Treatments	Relative risk reduction†	Comments	Source paper: First author (year), notes
ST elevation myocardial infarction (STEMI)			
Thrombolysis	31% (95% CI: 14,45)	<55 years: Odds Ratio (OR)=0.692; Relative Risk Reduction (RRR)=30.8% (95% CI: 14,45) 55-64 years: OR=0.736; RRR=26.4% (95% CI: 17,40) 65-74 years: OR=0.752; RRR=24.8% (95% CI: 15,37) > 75 years: OR=0.844; RRR=15.6% (95% CI: 4,30)	Estess (2002)[23]
Aspirin	23% (95% CI: 15,30)	RRR=23% (95% CI: 15,30): outcome is vascular deaths	ISIS-2 (1988)[24]
Primary CABG surgery	39% (95% CI: 23,52)	OR=0.61 (95% CI: 0.48,0.77); RRR=39% (95% CI: 23,52) on page 565, 0-5 year mortality	Yusuf (1994)[25]
Primary PCI	30% (95% CI: 15,42)	OR=0.70 (95% CI: 0.58,0.85); RRR=30% (95% CI: 15,42) outcome compares primary angioplasty to thrombolytics.	Keeley (2003)[26]
Beta blockers	4% (95% CI: -8,15)	OR=0.96 (95% CI: 0.85,1.08); RRR=4% (95% CI: -8,15) on page 1732	Freemantle (1999)[27]
ACE inhibitors	7% (95% CI: 2,11)	OR=0.93 (95% CI: 0.89,0.98); RRR=7% (95% CI: 2,11) for 30 day mortality in myocardial infarction	ACE Inhibitor Myocardial Infarction Collaborative Group (1998)[28]
Clopidogrel	3% (95% CI: 1,6)	RRR=3% (95% CI: 1,6) for 30 day mortality in myocardial infarction	Chen (2005) [29] Sabatine (2005)[30]
Hospital CPR	33% (95% CI: 10,36)	Survival at 24 hours estimated to be 32%, discharge to home at 21%, and 1 year survival to be 15% overall.	Tunstall-Pedoe (1992)[31] Nadkarni [32]

Table A2-2(continued)

Treatments	Relative risk reduction†	Comments	Source paper: First author (year), notes
Non-ST-segment elevation acute coronary syndrome (NSTEACS):			
Aspirin alone	15% (95% CI: 11,19)	OR=0.85 (95% CI: 0.49,0.95); RRR=15% (95% CI: 11,19). Outcome is vascular and nonvascular deaths on page 75. Assume appropriate for patients with NSTE-ACS.	Antithrombotic Trialists' Collaboration (2002)[33]
Aspirin & heparin	33% (95% CI: -2,56)	OR=0.67 (95% CI: 0.48,1.02); RRR=33% (95% CI: -2,56%) in Table 2. The study outcome is composite MI death and non-fatal MI; compares those on aspirin & heparin to aspirin only.	Oler (1996)[34]
Platelet glycoprotein IIB/IIIA inhibitors	9% (95% CI: 2,16)	OR=0.91 (95% CI: 0.84,0.98); RRR=9% (95% CI: 2,16). Study looked at acute coronary syndrome without persistent ST elevation.	Boersma (2002)[35]
Early PCI	32% (95% CI: 5,51)	OR=0.68 (95% CI: 0.49,0.95); RRR=32% (95% CI: 5,51)	RITA 3 (Fox 2005)[36]
Primary CABG surgery	39% (95% CI: 23,52)	OR=0.61 (95% CI: 0.48,0.77); RRR=39% (95% CI: 23,52) on page 565, 0-5 year mortality	Yusuf (1994)[25] Assumed similar as STEMI.
Clopidogrel	7% (95% CI: 2,11)	RRR=7% (95% CI: 2,11)	Yusuf (2001)[37]
Beta blockers	4% (95% CI: -8,15)	OR=0.96 (95% CI: 0.85,1.08); RRR=4% (95% CI: -8,15) on page 1732	Freemantle (1999)[27] Assumed similar as STEMI.
ACE inhibitors	7% (95% CI: 2,11)	OR=0.93 (95% CI: 0.89,0.98); RRR=7% (95% CI: 2,11) for 30 day mortality in myocardial infarction	ACE Inhibitor Myocardial Infarction Collaborative Group (1998)[28]

Table A2-2(continued)

Treatments	Relative risk reduction[†]	Comments	Source paper: First author (year), notes
Secondary prevention post myocardial infarction/revascularisation:			
Aspirin	15% (95% CI: 11,19)	OR=0.85 (95% CI: 0.49,0.95); RRR=15% (95% CI: 11,19). Outcome is vascular and nonvascular deaths on page 75. This data seems to be appropriate to this outcome in CHD patients.	Antithrombotic Trialists' Collaboration (2002)[33]
Beta blockers	23% (95% CI: 15,31)	OR=0.77 (95% CI: 0.69,0.85); RRR=23% (95% CI: 15,31) on page 1734. Odds of death in long term trials.	Freemantle (1999)[27]
ACE inhibitors or Angiotensin-II receptor antagonists	20% (95% CI: 13,26)	OR=0.80 (95% CI: 0.74,0.87); RRR=20% (95% CI: 13,26 on page 1577, death up to four years [endpoint of study looking at those with heart failure or LV dysfunction].	Flather (2000) [38]
Statins	24% (95% CI: 10,26)	RRR=24% (95% CI: 10,26)	Hulten (2006)[39]
		Intensive statin therapy in acute coronary syndromes.	Baigent(2004)[40]
Warfarin	22% (95% CI: 13,31)	OR=0.78 (95% CI: 0.67,0.90); RRR=22% (95% CI: 10,33)	Anand and Yusuf (1999)[41]
Rehabilitation	26% (95% CI: 10,39)	OR=0.74 (95% CI: 0.61,0.90); RRR=26% (95% CI: 10,39) in Figure 1, page 685 Taylor reference	Taylor (2004)[42]
Chronic stable coronary artery disease:			
CABG surgery years 0-5	39% (95% CI:23,52)	OR = 0.61 (95% CI: 0.48-0.77), RRR 39% (95% CI: 23,52) on page 565, 5 year mortality	Yusuf (1994)[25]

Table A2-2(continued)

Treatments	Relative risk reduction[†]	Comments	Source paper: First author (year), notes
CABG surgery years 6-10	32% (95% CI: 2,30)	OR = 0.83 (95% CI: 0.70-0.98), RRR 17% (95% CI: 2,30) on page 565, 10 year mortality. OR = 0.68 (95% CI: 0.56-0.83), RRR 32% (95% CI: 17,44) on page 565, 7 year mortality CABG compared to medical treatment	Yusuf (1994)[25]
Angioplasty	No effect		Boden (2007)[43]
Aspirin	15% (95% CI: 11,19)	OR=0.85 (95% CI: 0.49-0.95); RRR=15% (95% CI: 11,19). Outcome is vascular and nonvascular deaths on page 75.	Antithrombotic Trialists' Collaboration (2002)[33]
Statins	23% (95% CI: 10,26)	RRR=23% (95% CI 10,26) Standard dose statin therapy in coronary artery disease	Wilt (2004)[44]
ACE inhibitors/ARB	17% (95% CI: 6,28)	RRR=17% (95% CI 6,28)	Al-Mallah (2006)[45]
Heart failure in patients requiring hospitalisation or in the community:			
ACE inhibitors	20% (95% CI: 13,26)	OR=0.80 (95% CI: 0.74,0.87); RRR=20% (95% CI: 13,26) on page 1577 [death up to four years was study endpoint for those with heart failure or LV dysfunction]	Flather (2000)[38]
Beta blockers	35% (95% CI: 26,43)	OR=0.65 (95% CI: 0.57,0.74); RRR=35% (95% CI: 26,43): all cause mortality	Shibata (2001)[46]

Table A2-2(continued)

Treatments	Relative risk reduction[†]	Comments	Source paper: First author (year), notes
Spironolactone	30% (95% CI: 18,41)	OR=0.70 (95% CI: 0.59,0.82); RRR=30% (95% CI: 18,41) in those that had at least one cardiac related hospitalisation.	Pitt (1999)[47]
	31% (95% CI: 18,42)	OR=0.69 (95% CI: 0.58,0.82); RRR=31% (95% CI: 18,42) in entire study population consisting of those with community heart failure, page 711.	
Aspirin	15% (95% CI: 11,19)	OR=0.85 (95% CI: 0.49,0.95); RRR=15% (95% CI: 11,19). Outcome is vascular and nonvascular deaths on page 75.	Antithrombotic Trialists' Collaboration (2002)[33]
Statins	No effect		Kjekshus (2007)[48]
			Tavazzi (2008)[49]
Primary prevention therapies:			
Treatments for high blood pressure	13% (95% CI: 6,19)	OR=0.87 (95% CI: 0.81,0.94); RRR=13% (95% CI: 6,19) in those with high blood pressure without disease at entry. [RRR=29% (95% CI: 17,37) those with average blood pressure and CHD, treated with ACE inhibitors]	Law (2003)[50]
Statins	35% (95% CI: 11,52)	OR=0.65 (95% CI: 0.48,0.89); RRR=35% (95% CI: 11,52) for CHD mortality (only trials using statins), Figure 3 on page 4	Pignone (2000)[51]

Table A2-3. Data sources for treatment uptake levels in Poland 2005: Medical and surgical treatments included in the model

Treatments	Treatment Uptake in 2005; data for 1991 in parentheses	Source (year)
Acute myocardial infarction		
Thrombolysis	4,3% (10%)	National Registry of Acute Coronary Syndromes (2005) Pol-MONICA (1991)
Antiplatelet	81% (65%)	
Primary angioplasty	39% (0%)	
Primary CABG	1% (0%)	
Beta blockers	64% (38%)	
ACE inhibitors	62%(13%)	
Cardio-pulmonary resuscitation		
In the Community	16%	Rudner (2004)[21]
In Hospital	2%*	Bunch (2003)[52]
Secondary Prevention (POST-AMI)		
Aspirin	56% (55%)	WOBASZ (2003-2005) Pol-MONICA (1991)
Beta blockers	48% (30%)	WOBASZ (2003-2005)
ACE inhibitors	49% (0%)	WOBASZ (2003-2005)
Statins	35% (0%)	WOBASZ (2003-2005)
Warfarin	3% (0%)	WOBASZ (2003-2005)
Secondary Prevention (POST-REvascularisation)		
Aspirin	84% (0%)	WOBASZ (2003-2005)
Beta blockers	67% (0%)	WOBASZ (2003-2005)
ACE inhibitors	65% (0%)	WOBASZ (2003-2005)
Statins	66% (0%)	WOBASZ (2003-2005)
Warfarin	7% (0%)	WOBASZ (2003-2005)
Chronic Angina		
CABG surgery	11% (0%)	National Registry of Cardiosurgery (2005)
Aspirin in community	43% (?%)	WOBASZ (2003-2005)
Statins in community	21% (0%)	WOBASZ (2003-2005)
Unstable Angina		
Aspirin & Heparin	58% (10%)	PL-ACS (2005)

Table A2-3 (continued)

Treatments	Treatment Uptake in 2005; data for 1991 in parentheses	Source (year)
Aspirin alone	26% (30%)	PL-ACS (2005)
Platelet glycoprotein IIB/IIIA inhibitors	1% (0%)	PL-ACS (2005)
CABG surgery for UA	1% (0%)	PL-ACS (2005)
Angioplasty for UA	14% (0%)	PL-ACS (2005)
Heart Failure including a hospital admission		
ACE inhibitors	86% (0%)	HF2005
Beta blockers	61% (0%)	
Spironolactone	64% (0%)	
Aspirin	65% (0%)	
Statins	41% (0%)	
Heart Failure in the community		
ACE inhibitors	49% (0%)	HF2005
Beta blockers	46% (0%)	
Spironolactone	27% (0%)	
Aspirin	37% (0%)	
Statins	31% (0%)	
Hypertension treatments	45% (32%)	WOBASZ (2003-2005)
Hyperlipidaemia - 1' prevention		
Statins	11% (0%)	WOBASZ (2003-2005)

Uptake percentages as reported in source papers. Values may differ from those in Table 1 of the thesis, which report weighted averages for ALL age groups 25-84 years included in the Model.

* Assume approximately 2% of AMI admissions have primary ventricular fibrillation (Olmsted county)[51]

** Extrapolated from 1997-2002 data.

Table A2-4. Age-specific case fatality rates for each patient group

GROUP	AMI	Post AMI	Unstable Angina	CABG surgery	Angioplasty	Heart Hospital	Failure Community	Hypertension	Hypercholesteraemia
Interval	30 day	One year*	One year*	One year*	One year*	One year	One year	One year	One year
Mean	0.084	0.051	0.069	0.02	0.016	0.246	0.081	0.01	0.006
MEN									
25-34	0.011	0.008	0.016	0.003	0.003	0.034	0.011	0	0
35-44	0.012	0.009	0.024	0.005	0.005	0.068	0.022	0.001	0.001
45-54	0.023	0.017	0.034	0.007	0.007	0.096	0.032	0.002	0.002
55-64	0.054	0.034	0.056	0.012	0.012	0.14	0.045	0.006	0.006
65-74	0.101	0.073	0.07	0.023	0.025	0.283	0.093	0.014	0.014
75-84	0.164	0.122	0.091	0.042	0.042	0.337	0.111	0.035	0.035
85+	0.279	0.189	0.118	0.075	0.074	0.418	0.138	0.094	0.094
WOMEN									
25-34	0.011	0.004	0.016	0.003	0.003	0.034	0.011	0	0
35-44	0.013	0.006	0.024	0.005	0.005	0.068	0.022	0.001	0.001
45-54	0.026	0.01	0.034	0.007	0.007	0.096	0.032	0.001	0.001
55-64	0.061	0.019	0.056	0.012	0.012	0.14	0.045	0.002	0.002
65-74	0.114	0.084	0.07	0.023	0.027	0.222	0.081	0.007	0.007
75-84	0.167	0.116	0.091	0.042	0.039	0.289	0.094	0.021	0.021
85+	0.267	0.177	0.118	0.075	0.061	0.368	0.121	0.079	0.079
Source	USA Medicare	USA Medicare	Van Domberg[53]	USA Medicare	USA Medicare	USA Medicare	USA Medicare	NHANES & Vital Statistics	

Table A2-5. Beta coefficients for major risk factors

Estimated β coefficients from multiple regression analyses for the relationship between absolute changes in population mean risk factors and percentage changes in coronary heart disease mortality for men and women, stratified by age. Data sources, values and comments.

Table A2-5-1 Systolic blood pressure

Systolic blood pressure	**Age group (years)**				
	25-44	**45-54**	**55-64**	**65-74**	**75+**
Men (hazard ratio per 20 mmHg)	0.49	0.49	0.52	0.58	0.65
Men (log hazard ratio per 1 mmHg)	**-0.036**	**-0.035**	**-0.032**	**-0.027**	**-0.021**
Minimum	*-0.029*	*-0.028*	*-0.026*	*-0.022*	*-0.017*
Maximum	*-0.043*	*-0.042*	*-0.039*	*-0.032*	*-0.025*
Women (hazard ratio per 20 mmHg)	0.40	0.40	0.49	0.52	0.59
Women (log hazard ratio per 1 mmHg)	**-0.046**	**-0.046**	**-0.035**	**-0.032**	**-0.026**
Minimum	*-0.037*	*-0.037*	*-0.028*	*-0.026*	*-0.021*
Maximum	*-0.055*	*-0.055*	*-0.042*	*-0.039*	*-0.031*

Source: Prospective studies collaborative meta-analysis, Lancet 2002[11]

Units: Percentage change in CHD mortality per 20 mmHg change in systolic blood pressure

Strengths: Large dataset, includes US data, adjusted for regression dilution bias, consistent with randomised controlled trials, results stratified by age and sex, with 95% confidence intervals

Limitations: Some publication bias still possible

Table A2-5-2 Cholesterol

Cholesterol	**Age groups (years)**					
	25-44	**45-54**	**55-64**	**65-74**	**75-84**	**85+**
Mortality reduction per 1 mmol/l						
Men	0.55	0.53	0.36	0.21	0.21	0.21
Women	0.57	0.52	0.35	0.23	0.23	0.23
Log coefficient						
Men	**-0.799**	**-0.755**	**-0.446**	**-0.236**	**-0.117**	**-0.083**
Minimum	*-0.639*	*-0.604*	*-0.357*	*-0.189*	*-0.093*	*-0.067*
Maximum	*-0.958*	*-0.906*	*-0.536*	*-0.283*	*-0.140*	*-0.100*
Women	**-0.844**	**-0.734**	**-0.431**	**-0.261**	**-0.174**	**-0.051**
Minimum	*-0.675*	*-0.587*	*-0.345*	*-0.209*	*-0.139*	*-0.041*
Maximum	*-1.013*	*-0.881*	*-0.517*	*-0.314*	*-0.209*	*-0.062*

Source: Prospective studies collaborative meta-analysis, Lancet 2007[54]

Units: Percentage change in CHD mortality per 1 mmol/l change in total cholesterol

Strengths: Includes US data, adjusted for regression dilution bias, includes randomised controlled trials, RCT values consistent with observational data, results stratified by age and sex, with 95% confidence intervals

Limitations: Some publication bias still possible

Table A2-5-3 Body mass index

Body Mass Index (BMI)	**Age groups (years)**				
	<44	**45-59**	**60-69**	**70-79**	**80+**
James et.al (2004):					
Hazard ratio	0.89	0.91	0.95	0.96	0.97
Risk reduction† per 1 kg/m^2	0.11	0.09	0.05	0.04	0.03
Age gradient (45-59 as reference)	1.22	**1.00**	0.56	0.44	0.33
Bogers (2006):					
Relative risks, CHD deaths per 5 BMI units (kg/m^2)		**1.16**			
Relative risks per 1 kg/m^2 applying age gradients from James et.al	1.04	1.03	1.02	1.01	1.01
Log coefficients	**0.0363**	**0.0297**	**0.0165**	**0.0132**	**0.0099**
Minimum	*0.0255*	*0.0209*	*0.0116*	*0.0093*	*0.0070*
Maximum	*0.0466*	*0.0381*	*0.0212*	*0.0169*	*0.0127*

Source: Bogers et al (2006)[55], James et al (2004)[56]

Units: Percentage change in CHD mortality per 1 kg/m^2 change in BMI

Strengths: Large number of studies included. Adjusted for blood pressure, total cholesterol, and physical activity. 95% confidence intervals included.

Limitations: Observational data; age gradient applied from James study

Table A2-6. Relative Risks for CHD used in the IMPACTSEC model for Smoking, Diabetes and Physical Inactivity (Best, Minimum and Maximum Estimates from the InterHeart Study[12])

	Both sexes		**Men**		**Women**	
Lifestyle factors:	**Young**	**Old**	**≤ 55 years**	**> 55 years**	**≤ 65 years**	**> 65 years**
Smoking	**3.33 (2.86-3.87)**	**2.44 (2.10-2.84)**	**3.33 (2.80-3.95)**	**2.52 (2.15-2.96)**	**4.49 (3.11-6.47)**	**2.14 (1.35-3.39)**
Exercise	**0.95 (0.79-1.14)**	**0.79 (0.66-0.94)**	**1.02 (0.83-1.25)†**	**0.79 (0.66-0.96)**	**0.74 (0.49-1.10)**	**0.75 (0.46-1.22)**
Alcohol	1.00 (0.85-1.17)	0.85 (0.73-1.00)	1.03 (0.87-1.23)	0.86 (0.73-1.01)	0.74 (0.41-1.31)	0.83 (0.49-1.42)
Hypertension	2.24 (1.93-2.60)	1.72 (1.52-1.95)	1.99 (1.66-2.39)	1.72 (1.49-1.98)	2.94 (2.25-3.85)	1.82 (1.39-2.38)
Diabetes	**2.96 (2.40-3.64)**	**2.05 (1.71-2.45)**	**2.66 (2.04-3.46)**	**1.93 (1.58-2.37)**	**3.53 (2.49-5.01)**	**2.59 (1.78-3.78)**
Abdominal obesity	1.79 (1.52-2.09)	1.50 (1.29-1.74)	1.83 (1.52-2.20)	1.54 (1.30-1.83)	1.58 (1.14-2.20)	1.22 (0.88-1.70)
Psychosocial	2.87 (2.19-3.77)	2.43 (1.86-3.18)	2.62 (1.91-3.60)	2.45 (1.82-3.29)	3.92 (2.26-6.79)	2.31 (1.22-4.39)
High ApoB/ApoA1 ratio	4.35 (3.49-5.42)	2.50 (2.05-3.05)	4.16 (3.19-5.42)	2.51 (2.00-3.15)	4.83 (3.19-7.32)	2.48 (1.60-3.83)

Smoking, adverse lipid profile, hypertension, and diabetes had a greater relative effect on risk of acute myocardial infarction in younger than older individuals. †The InterHeart study quoted a value of only 1.02 for exercise in men aged ≤ 55 years. This was clearly an outlier. We have therefore assumed a value of 0.77 in line with men and women in the other age groups, and consistent with most other studies.

Table A2.7 Main assumptions and overlap adjustments used in the Polish IMPACT Model

Treatment category	Assumptions and Overlap Adjustments	**Justification**
Post-AMI patients	Assume 25% already counted as HF patients	Unal (2004)[4]
	Therefore assume residual case fatality halved, having transferred these HF patients to the HF group	Unal (2004)[4]
Post-CABG patients	Assume 2/3 had MI, already counted as Post AMI	Unal (2004)[4]
Post-PCI survivors	Assume 50% had prior AMI, already counted as Post AMI	Unal (2004)[4]
	Assume 25% also had CABG, thus already counted as Post CABG	NHDS
	Assume 25% had prior PCI, i.e. repeats, already counted	NHDS
Chronic angina treatment: PCI patients progressing to CABG surgery	Assume that 20% of PCI go to CABG	NHDS
Angina in the community	Start with the total patient numbers with angina in the community, based on NHANES prevalence	Capewell (2000)[3]
	Then deduct patients counted elsewhere:	
	-Patients already treated for unstable angina in hospital,	
	-50% of those receiving CABG for angina	
	-50% of those receiving secondary prevention post AMI/post CABG/Post Angioplasty,	
Heart failure in the community	Based on NHANES prevalence	NHANES 1999-2000
	-Assume 50% of heart failure is due to CHD	
	-Deduct patients treated for severe heart failure in the hospital (already counted)	

Table A2-7 (continued)

Treatment category	Assumptions and Overlap Adjustments	**Justification**
Hypertension treatment: overlaps with other CHD patient groups	Total hypertensive patient numbers in community calculated, then deduct: -50% of post AMI patients -50% of community angina patients -50% of community heart failure patients	NHANES 1999-2000
Fall in population blood pressure	Estimate the number of DPPs by hypertension treatment -Then subtract this from the total DPPs attributed to the secular fall in population BP	Capewell *(*1999)[57]

AMI : acute myocardial infarction, CABG: coronary artery bypass graft surgery, CHD:coronary heart disease, DPPs:deaths prevented or postponed, HF: heart failure, NHDS: US National Hospital Discharge Survey; NHANES: National Health and Nutrition Examination Survey, and PCI: percutaneous coronary intervention.

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A3. Age standardized CHD mortality rates by age, gender and Index of Multiple Deprivation, England 1982-2006

Table A3-1 Age standardized CHD mortality rates by age, gender and Index of Multiple Deprivation, England 1982-2006

	Year	Least deprived (Q1)	Q2	Q3	Q4	Most deprived (Q5)	**England**	Absolute gap (Q5-Q1)	Rate Ratio (Q5/Q1)	95% CI for rate ratio
Men	**1982**	577.8	645.8	702.5	778.3	878.3	**719.5**	300.5	1.52	*(1.50 - 1.54)*
	1983	568.0	639.9	697.0	773.0	878.7	**713.8**	310.7	1.55	*(1.53 - 1.57)*
	1984	562.6	639.5	699.2	778.3	886.2	**715.2**	323.6	1.58	*(1.56 - 1.60)*
	1985	552.0	627.4	686.6	768.7	880.8	**704.6**	328.8	1.60	*(1.58 - 1.62)*
	1986	537.2	611.6	669.7	750.5	867.4	**688.1**	330.2	1.61	*(1.59 - 1.64)*
	1987	518.3	586.4	639.8	718.0	839.3	**660.4**	321.0	1.62	*(1.60 - 1.64)*
	1988	494.2	563.6	620.7	690.2	815.9	**636.2**	321.7	1.65	*(1.63 - 1.67)*
	1989	476.0	546.3	596.6	667.6	795.5	**615.1**	319.5	1.67	*(1.65 - 1.69)*
	1990	462.5	533.2	586.7	654.9	777.0	**601.0**	314.5	1.68	*(1.66 - 1.70)*
	1991	453.3	519.9	568.3	641.9	759.7	**586.1**	306.4	1.68	*(1.65 - 1.70)*
	1992	448.8	510.0	560.0	631.7	746.9	**576.3**	298.1	1.66	*(1.64 - 1.69)*
	1993	435.4	487.7	533.8	603.7	720.6	**552.5**	285.3	1.66	*(1.63 - 1.68)*
	1994	419.9	468.9	513.6	583.8	693.6	**531.8**	273.7	1.65	*(1.63 - 1.68)*
	1995	398.1	444.0	488.8	555.9	658.8	**504.6**	260.7	1.65	*(1.63 - 1.68)*
	1996	376.7	424.0	468.2	534.5	635.5	**482.8**	258.8	1.69	*(1.66 - 1.71)*
	1997	356.7	405.2	447.7	508.1	612.0	**460.5**	255.4	1.72	*(1.69 - 1.74)*
	1998	336.6	380.9	424.4	482.8	586.1	**436.3**	249.6	1.74	*(1.72 - 1.77)*
	1999	318.9	361.6	403.6	461.0	557.8	**414.5**	238.9	1.75	*(1.72 - 1.78)*
	2000	299.4	340.5	382.8	441.0	531.3	**392.6**	231.8	1.77	*(1.75 - 1.80)*
	2001	281.6	324.8	361.9	424.7	509.6	**373.6**	228.0	1.81	*(1.78 - 1.84)*
	2002	266.1	311.1	343.6	404.4	493.5	**356.4**	227.4	1.85	*(1.82 - 1.88)*
	2003	251.6	293.3	324.0	381.4	469.0	**336.3**	217.4	1.86	*(1.83 - 1.89)*
	2004	234.7	274.1	305.1	355.0	442.1	**314.7**	207.4	1.88	*(1.85 - 1.92)*
	2005	217.5	250.0	284.4	331.2	412.6	**291.5**	195.1	1.90	*(1.86 - 1.93)*
	2006	202.1	232.1	263.6	310.8	391.7	**272.2**	189.5	1.94	*(1.90 - 1.97)*
	Overall % fall	-65.0	-64.1	-62.5	-60.1	-55.4	**-62.2**	-36.9		
	Average annual % change (AAPC)*	-4.3	-4.2	-4.0	-3.7	-3.3	**-4.0**			
	95% CI for AAPC	*(-4.1 to -4.5)*	*(-4.0 to -*	*(-3.7 to -*	*(-3.5 to -*	*(-3.2 to -3.5)*	**(-3.8 to -4.1)**			

Notes: Rates are three year moving averages, central year reported. AAPC: average annual percent change. Rates adjusted to European standard population.

Table A3-1 (continued)

	Year	Least deprived	Q2	Q3	Q4	Most deprived	**England**	Absolute gap (Q5-1)	Rate Ratio (Q5/Q1)	95% CI for rate ratio
Women	**1982**	250.2	284.1	303.8	340.4	410.9	**320.7**	160.7	1.64	*(1.62 - 1.67)*
	1983	247.0	282.9	304.8	342.9	414.6	**321.3**	167.6	1.68	*(1.65 - 1.70)*
	1984	249.1	286.0	309.2	350.1	419.7	**325.5**	170.6	1.68	*(1.66 - 1.71)*
	1985	247.3	283.8	306.8	349.5	417.9	**323.3**	170.6	1.69	*(1.67 - 1.72)*
	1986	242.0	276.3	301.5	342.5	411.9	**316.7**	170.0	1.70	*(1.68 - 1.73)*
	1987	233.5	266.5	291.5	330.5	402.8	**306.4**	169.3	1.73	*(1.70 - 1.75)*
	1988	226.4	258.1	283.7	322.2	397.1	**298.6**	170.7	1.75	*(1.73 - 1.78)*
	1989	221.8	252.8	275.8	315.5	389.2	**291.7**	167.4	1.75	*(1.73 - 1.78)*
	1990	218.2	249.8	272.3	313.0	383.7	**287.8**	165.5	1.76	*(1.73 - 1.79)*
	1991	214.6	247.1	268.3	307.2	376.7	**282.9**	162.1	1.76	*(1.73 - 1.78)*
	1992	212.5	244.8	265.3	306.1	370.4	**279.7**	157.9	1.74	*(1.72 - 1.77)*
	1993	206.3	234.6	254.6	294.0	354.6	**268.3**	148.2	1.72	*(1.69 - 1.74)*
	1994	198.1	224.6	244.3	283.4	338.3	**257.0**	140.3	1.71	*(1.68 - 1.73)*
	1995	187.0	212.7	232.6	267.9	321.2	**243.3**	134.3	1.72	*(1.69 - 1.75)*
	1996	178.1	202.2	222.8	256.3	308.2	**232.3**	130.1	1.73	*(1.70 - 1.76)*
	1997	169.2	192.8	214.5	247.2	296.0	**222.5**	126.8	1.75	*(1.72 - 1.78)*
	1998	159.2	181.1	203.5	234.7	282.8	**210.6**	123.6	1.78	*(1.75 - 1.81)*
	1999	149.2	170.7	192.6	222.5	267.5	**198.7**	118.2	1.79	*(1.76 - 1.82)*
	2000	141.2	159.1	181.6	208.6	254.1	**186.9**	112.9	1.80	*(1.77 - 1.83)*
	2001	135.0	151.6	171.3	199.7	243.6	**177.9**	108.6	1.80	*(1.77 - 1.84)*
	2002	129.1	146.0	164.3	193.9	237.6	**171.6**	108.6	1.84	*(1.81 - 1.87)*
	2003	121.5	138.6	155.1	183.3	226.5	**162.2**	105.0	1.86	*(1.83 - 1.90)*
	2004	113.3	129.5	146.2	171.0	212.4	**151.6**	99.1	1.87	*(1.84 - 1.91)*
	2005	103.6	119.1	134.3	157.4	195.4	**139.0**	91.8	1.89	*(1.85 - 1.92)*
	2006	96.4	110.0	124.2	147.3	182.9	**129.2**	86.6	1.90	*(1.86 - 1.94)*
	Overall % fall	-61.5	-61.3	-59.1	-56.7	-55.5	**-59.7**	-46.1		
	Average annual % change	-3.9	-3.9	-3.7	-3.4	-3.3	**-3.7**			
	95% CI for AAPC	*(-3.6 to -4.2)*	*(-3.5 to -*	*(-3.3 to -*	*(-3.1 to -*	*(-3.2 to -3.5)*	**(-3.4 to -4.0)**			

Notes: Rates are three year moving averages, central year reported. AAPC: average annual percent change. Rates adjusted to European standard population.

A4. The English IMPACT$_{SEC}$ Model: methods and data sources

We have extended the IMPACT model to accommodate sub-national variation in CHD mortality trends by socioeconomic circumstances (IMPACT$_{SEC}$ model). We used the Index of Multiple Deprivation 2007 (IMD) quintiles as a proxy indicator of socioeconomic circumstances. This model examines the effects of changes in treatment uptake and risk factor trends on changes in mortality from coronary heart disease (CHD) among adults in England aged 25 years and over, stratified into equal quintiles by population size. The tables included in this appendix provide details about the sources and methods that were used.

Only those aspects of the IMPACT SEC model that differ from the IMPACT model described in chapter 6 and appendix A2 will be discussed here.

Data sources used to estimate the observed and expected number of deaths from CHD for 2000 and 2007 are shown in Table A4-1. The expected number of CHD deaths in 2007 was calculated by multiplying the age-sex-IMD quintile specific mortality rates from CHD in 2000 by the population counts for 2007 in that age-sex-IMD quintile stratum. Summing over all strata then yielded the expected number of deaths. The difference between the number of expected and observed deaths from CHD represented the mortality fall, or the DPPs in 2007 relative to 2000.

Data sources for estimating eligible patients for treatments included in the model is available in Table A4-1, and their uptake levels in table A4-2.

Sources of relative risk reductions for treatments and effects measures for risk factors are the same as the one used in the Polish IMPACT models (appendix A2)

Data on risk factor sources and their levels is available in tables A4-3 and A4-4

Details on model fit are available in table A4-5

A4.1 IMPACT SEC specific issues

Allocating areas to socioeconomic quintiles using the Index of Multiple Deprivation, 2007

The Index of Multiple Deprivation (IMD) is a composite index of relative deprivation at small area level based on seven domains: income; employment; health deprivation and disability; education, skills and training; barriers to housing and services; crime and disorder; and living environment.[1] The IMD 2007 score of all small areas in England (average population 1,500) were ranked in ascending order and grouped into equal quintiles (about 6,500 areas in each), with quintile one (IMDQ1) including the most affluent and quintile five (IMDQ5) the most deprived areas. Based on their postcode of residence, patients treated in hospital (e.g. recorded in Hospital Episode Statistics) or in the community (e.g. in the General Practice Research Database) were matched via their area of residence to the corresponding deprivation quintile by the data providers to protect patient anonymity. Mortality counts were similarly aggregated into deprivation quintiles by the Office for National Statistics before being released to us for research purposes.

As the IMD 2007 includes rates of premature total mortality in the health domain, its use to quantify health inequalities risks a tautology. However UK studies have shown that removing the health

domain had little effect on either the assignment of areas into their deprivation quintile or the relationship between area-based deprivation and health.[2]

Conceptually, the IMD 2007 is a measure of deprivation, not a measure of affluence. Hence, areas with the lowest scores are not necessarily the most affluent; rather they have the lowest concentration of deprived people. In this paper for clarity and to easily distinguish between the extreme ends of the deprivation spectrum, we have used the term 'most affluent' and 'most deprived' rather than 'least deprived' and 'most deprived'.

Uncertainty analyses

We implemented uncertainty analysis in Excel using Ersatz (version 1.0 available at http://www.epigear.com), an add-in that allows probabilistic bootstrapping in Excel. Ersatz allows repeated random draws from specified distributions for input variables and then calculates the 95% uncertainty intervals from the realised values of the output variable (deaths prevented or postponed). For the $IMPACT_{SEC}$ model, we calculated the uncertainty intervals based on 1000 draws. The parameter distributions used for the input variables are shown in Table A4-6.

Estimating DPPs attributed to treatments: Net effects and patient groups overlaps.

"Net effects"

As all treatments were in use in 2000, the net benefit of an intervention in 2007 was calculated by subtracting the expected number of deaths prevented if the uptake rates in 2000 remained constant from the estimated number of deaths prevented calculated using the 2007 uptake rates.

Example 1: Net effects for treatments

Calculating net effects for clopidogrel use in STEMI cases in men aged 75-84 in the most affluent quintile

With an estimated total of 1,440 men aged 75-84 in the most affluent quintile (of whom 40% were assumed to be STEMI cases), 89% uptake, a relative risk reduction of 3%, a one-year case fatality rate of 34%, and 100% compliance, the total number of DPPs in 2007 was calculated as:

Patient numbers × treatment uptake$_{2007}$ × relative mortality reduction × one year case fatality

= (1,440 × 40%) × **89**% × 3% × 34% ≈ 5 DPPs

Applying the uptake rate in 2000 (31%) gave a total of 2 DPPs:

Patient numbers × treatment uptake$_{2000}$ × relative mortality reduction × one year case fatality

= (1440 × 40%) × **31**% × 3% × 34% ≈ 2 DPPs

The net DPPs were therefore:

Net DPPs = DPPs using uptake$_{2007}$ – DPPs using uptake$_{2000}$

= 5 –2 = 3

'Fixed gradients' for measuring risk factor change between two time points for deprivation quintiles

The annual sample size of the Health Survey for England (HSfE), roughly 14,000 adults aged 16 years and over, was not large enough to provide accurate/precise estimates of risk factor levels, and hence rates of change over time by age, sex, and deprivation quintiles (70 groups in total). We considered three options for estimating risk factor change as key inputs into the regression and PARF deaths prevented or postponed calculations:

Option 1: using single-year estimates for the base and final year (2000 and 2007 respectively). Both surveys, however, were half the usual adult size due to boost samples for population sub-groups.

Option 2: using estimates based on three-year averages with pooled 1999-2001 survey data for the base year (2000) and 2005-7 for the final year (2006 as the mid-year). Estimates of risk factor change over 2000-6 were scaled up by a factor of 8/7 (i.e. number of years between 2000 and 2007 divided by the observed number of years).

Option 3: the 'fixed gradient approach' (discussed in detail below).

The fixed gradient approach was based on the assumption that changes in pace and direction for each deprivation quintile were similar and therefore, most accurately measured by the overall national rates of change (across 14 age-sex groups). If this assumption holds, then relatively stable and plausible estimates for each quintile could be derived by scaling the national age-sex risk factor levels up or down using a fixed ratio/gradient.

The fixed gradient was derived by pooling together survey data for all available years from 2000 to 2007 to calculate risk factor estimates by age, sex, and deprivation fifths. Then the pooled national estimate for 14 age-by-sex groups was set notionally to one, and the corresponding estimates for each deprivation quintile re-indexed to be below or above one (i.e. expressing the ratio of the deprivation quintile to national estimate). These index rates for each of the 70 breaks were then applied to the single year national estimates to derive the corresponding 70 risk factor levels for that year. The fixed gradient was applied to both the start and end years of the model. An illustrative example, using the population-attributable risk fraction (PARF), is set out below.

EXAMPLE: Fixed gradient for change in smoking prevalence in men aged 45-54

Step 1

Using the pooled 2000-7 HSfE data the national estimate of current smoking was 25.7% for men aged 45-54. Estimates by deprivation quintile ranged from 14.0% for men in the most affluent quintile (IMDQ1) to 46.5% in the most deprived (IMDQ5). The best estimate, obtained from the InterHeart study, of the relative risk (RR) of smoking was 3.3.[9] Using the smoking prevalence (P) and the RR (assumed the same across deprivation quintiles) we calculated the PARF for England as a whole and each deprivation quintile using the formula:

$$PARF = [P \times (RR - 1)]/[1 + P \times (RR - 1)]$$

Applying step 1: Calculate the PARF gradient using 2000-7 pooled survey data

Men 45-54	England 2000-7	IMDQ1 2000-7	IMDQ2 2000-7	IMDQ3 2000-7	IMDQ4 2000-7	IMDQ5 2000-7
Proportion smokers (P)	0.2569	0.1398	0.1949	0.2668	0.2882	0.4652
RR	3.3	3.3	3.3	3.3	3.3	3.3
PARF	0.3744	0.2457	0.3123	0.3834	0.4017	0.5201
Gradient in PARF	1	0.656	0.834	1.024	1.073	1.389

The PARF calculated using pooled data at the national level was then set notionally to one, and the corresponding values for each deprivation quintile re-indexed to be below or above one. For example, the pooled gradient in the PARF for men aged 45-54 in Q1 was estimated to be 0.2457/0.3744 = 0.656.

Step 2

Using the HSfE data for the start and final year of the model we then derived the national PARF for 14 age-by-sex groups. The national PARF for men aged 45-54 based on prevalence (P) of 28.3% and RR of 3.3 in 2000 was 0.3976; a prevalence of 25.1% in 2007 gave a PARF of 0.3688.

Applying step 2: Calculate the national PARF in base and final year

Men 45-54	England 2000	England 2007
Proportion smokers (P)	0.2832	0.2508
RR	3.3	3.3
PARF	0.3976	0.3688

Step 3

The fixed gradient (Step 1) was then applied to the national PARF (Step 2) to produce estimates of the PARF for each deprivation quintile, separately for the base and final years of the model. For example, for men aged 45-54 in Q1 the 2000 estimate of the PARF was equal to 0.3976 (national PARF) multiplied by the gradient (0.656), to give an estimate of 0.2608. The 2007 estimate was equal to 0.3688 (national PARF) multiplied by the fixed gradient (0.656), to give an estimate of 0.2420.

Applying step 3: Estimate the PARF by deprivation quintiles for single years 2000 and 2007 using fixed gradient

Men 45-54	England 2000-7	IMDQ1 2000-7	IMDQ2 2000-7	IMDQ3 2000-7	IMDQ4 2000-7	IMDQ5 2000-7
PARF 2000	0.3976	0.2608	0.3316	0.4071	0.4265	0.5523
PARF 2007	0.3688	0.2420	0.3076	0.3376	0.3957	0.5124

Step 4: Calculating the DPPs

The formula for calculating DPPs using the change in PARF approach was as follows:

Adjusted CHD deaths in 2000 × difference between the PARF in 2000 and 2007

Adjusted CHD deaths in 2000 × ($PARF_{2000}$ – $PARF_{2007}$)

Applying step 4: Estimate the DPPs due to change in PARF between 2000 and 2007

Men 45-54	**England 2000-7**	**IMDQ1 2000-7**	**IMDQ2 2000-7**	**IMDQ3 2000-7**	**IMDQ4 2000-7**	**IMDQ5 2000-7**
CHD mortality rate (2000)†	0.9131	0.5434	0.6644	0.8177	1.1173	1.6448
Population (2007)	3284291	736444	700676	660481	611424	575266
Adjusted deaths (2007)	3035	400	466	540	683	946
PARF 2000	0.3976	0.2608	0.3316	0.4071	0.4265	0.5523
PARF 2007	0.3688	0.2420	0.3076	0.3776	0.3957	0.5124
DPPs in 2007	**93‡**	**8**	**11**	**16**	**21**	**38**

† Rate per 1000

‡ The total DPPs for England was based on the sum of the DPPs across the deprivation quintiles.

We tested all three options and selected Option 3 ('fixed gradient' approach). This method had the advantage of reducing the number of data breaks to a maximum of 14 (age by sex) for any single HSfE year and instead of discarding the survey information in the intermediate years, used the whole data series to improve and stabilise the 70 estimates. The disadvantage was that the assumption of a fixed gradient for each age-by-sex group remaining constant over time may not hold (e.g. the difference in risk factor level between a deprivation quintile and the national rate may be considerably larger in 2000 than in 2007).

Patient overlaps:

To avoid double counting of patients treated for two or more conditions within the year (e.g. heart failure develops within 1 year after myocardial infarction in approximately 30% of survivors) we quantified overlaps between different groups and made appropriate adjustments. Overlap adjustments were based on estimating the patient counts for each condition separately, and the counts of patients with two or more of the target conditions. The latter, or the probabilities of events intersecting, were then used to adjust single patient counts into unique non-overlapping counts by condition.

We constructed nine non-overlapping patient groups. Following the basic logic of the natural history of coronary disease, patients recorded as having two or more conditions were allocated to the condition that was further along the disease pathway. For instance, if an individual had both chronic angina and heart failure, they were allocated to heart failure.

Therefore, to avoid double counting, potential overlaps between different groups of patients were identified and appropriate adjustments made by subtracting one group from another. For instance, we can subtract the number of severe heart failure patients treated in hospital from the total number of heart failure patients in the community (because community heart failure patients could be admitted to hospital on one or more occasions). Details of the overlap adjustments are available in Table A4-7 and figure A4-1.

References for the English $IMPACT_{SEC}$ model appendix

1. Noble M, mcLennan D, Wilkinson K et al. The English Indices of Deprivation 2007. Department for Communities and Local Government.
2. Adams J, White M. Removing the health domain from the Index of Multiple Deprivation 2004 - effect of measured inequalities in census measure of health. Journal of Public Health 2006;28:379-83.
3. Craig R, Mindell J. Health Survey for England 2006. 2008. London, United Kingdom, The Information Centre.

A4.2 Data Tables

Table A4-1. Population and patient data sources used in the IMPACTSEC model

Information	Source
Population data	
Population counts and CHD deaths stratified by age, sex, and Index of Multiple Deprivation quintiles	Office for National Statistics (ONS):(2000: ICD9 410-414,429) (2007: ICD10 I20-I25)
Number of patients admitted to hospital:	
Myocardial infarction (MI)	Hospital Episode Statistics (HES). Emergency admissions with a primary diagnosis of MI (ICD10: I21). (www.hesonline.nhs.uk). The ratio of MI admissions to STEMI and nSTEMI cases taken as 40/60.13Individual level data for 1998 to 2007 supplied by The NHS Information Centre (reference No ET2323).
Angina pectoris	HES. Emergency admissions with a primary diagnosis of angina pectoris (ICD10: I20).
Heart failure	HES. Admissions with a primary diagnosis of heart failure (ICD10: I50).
Number of patients undergoing revascularisation:	
CABG	HES. OPCS Classification of Surgical Operations and Procedures – Fourth Revision (OPCS-4) K40-K46.
PCI	HES. OPCS Classification of Surgical Operations and Procedures – Fourth Revision (OPCS-4) OPCS K49, K50.1, K75.
Patients in the community eligible for secondary prevention therapies:	
Post MI Angina without MI Heart failure	General Practice Research Database (GPRD) (http://www.gprd.com/home/).
Cardiac rehabilitation (CR)	Number enrolled in CR programmes adapted from the National Audit of Cardiac Rehabilitation (http://www.cardiacrehabilitation.org.uk)14
Patients eligible for primary prevention therapies:	
Lipid-lowering drugs	Prevalence of never having had angina or heart attack and currently taking lipid lowering drugs prescribed by a doctor from the Health Survey for England (HSfE 1998, 2003, and 2006) (http://www.ic.nhs.uk/statistics-and-data-collections/health-and-lifestyles-related-surveys/health-survey-for-england)
Hypertension treatment	Prevalence of never having had angina or heart attack and currently taking medication specifically prescribed to treat high blood pressure from the Health Survey for England (HSfE 1998, 2003, and 2006)

Table A4-2. Data sources for treatment uptake levels for the Medical and surgical treatments included in the model

Information	Source
Medication use in hospital:	
(ST-segment elevation myocardial infarction): Aspirin Beta Blockers ACE I or Angiotensin-II receptor antagonists (ARB) Thrombolysis	Myocardial Ischaemia National Audit Project (MINAP) 2003to2007. (http://www.rcplondon.ac.uk/clinical-standards/organisation/partnership/Pages/MINAP-.aspx). STEMI cases defined by the final diagnosis field (includes those with threatened infarction).
Non-ST-segment elevation acute coronary syndrome (NSTEACS): Aspirin without heparin Aspirin & heparin Platelet glycoprotein IIB/IIIA inhibitors Beta Blockers ACE I/ARB Clopidogrel	MINAP 2003 to 2007. nSTEMI cases defined by the final diagnosis field.
Heart failure due to CHD: Aspirin† Beta blockers†† ACE I/ARB†† Spironolactone††	† Assumed equal to post MI rates in the community obtained using the General Practice Research Database (GPRD) (http://www.gprd.com/home/) †† NHS Heart Failure Survey 2005.15 Start year values for beta-blockers, ACE I/ARB and spironolactone assumed to be to 10% lower than 2005 values.
In-hospital cardio-pulmonary resuscitation (CPR)	MINAP 2003 to 2007.
CPR in the community	Net benefits assumed to be zero.
Cardiac rehabilitation for MI and revascularisation survivors	Number enrolled in CR programmes adapted from the National Audit of Cardiac Rehabilitation (http://www.cardiacrehabilitation.org.uk)14

Table A4-2(Continued)

Information	Source
Medication use in the community:	General Practice Research Database (GPRD) (http://www.gprd.com/home/).
Post MI and revascularisation survivors, chronic stable coronary artery disease (CAD), heart failure	
Aspirin	
Beta blockers	
ACE I/ARB	
Statins	
Warfarin	
Spironolactone	
Primary prevention therapies:	
Lipid-lowering drugs	Prevalence of never having had angina or heart attack and currently taking lipid lowering drugs prescribed by a doctor from the Health Survey for England (HSfE 1998, 2003, and 2006).
Anti-hypertensive medication	Prevalence of never having had angina or heart attack and currently taking medication specifically prescribed to treat high blood pressure from the Health Survey for England (HSfE 1998, 2003, and 2006).

Table A4-3 Risk factors – variable definitions and source

The Health Survey for England (HSfE), an annual nationwide household survey of the English population, has been described in detail elsewhere.[3] Briefly, members of a stratified random sample (drawn from the Postcode Address File) that is socio-demographically representative of the English population were invited to participate. The annual household response rate was 75% in 2000, falling steadily to 66% in 2007. Data were collected at two visits: an interviewer's visit, during which a questionnaire was administered, followed by a visit from a trained nurse for all those interviewed who agreed. The nurse visit, which did not take place in 2004 among the general population sample, includes measurements and collection of blood, as well as additional questioning including use of prescribed medication (1998, 2003, and 2006). The magnitude of risk factor change from 2000 to 2007 used for the calculation of DPPs (see Examples 2 and 3) was estimated using a 'fixed gradient' approach across deprivation quintiles to maximise precision. For details on this approach see above. Risk factor levels in 2000 and 2007 by deprivation quintiles and sex are shown in Table A4-5.

Table A4-3 Risk factors – variable definitions and source (continued)

Risk factor	HSfE survey year	Description
Current cigarette smoking	2000-7	Self-reported status
SBP (mmHg)	All years between 2000-7 except 2004	Calculated as the mean of the 2nd and 3rd readings for those who had not eaten, consumed alcohol or smoked in the 30 minutes prior to measurement
Body Mass Index	2000-7	Weight (kg) divided by height squared (m2) for all respondents with valid height and weight measurements. Those reporting taking blood pressure lowering drugs were included
Total cholesterol (mmol/l)	1998,2003,2006	Those reporting taking lipid lowering drugs were included
Diabetes	1998,2003,2006	Those reporting diabetes that was doctor-diagnosed, excluding women who had only had diabetes during pregnancy
Physical activity	1998,2003,2006	High levels defined as spending 30 minutes or more of moderate or vigorous activity on at least five days per week. Occupational activity was excluded.
Fruit and vegetable consumption	2001-7	Measured in portions per day

Table A4-4. Risk factor levels in 2000 and 2007 by sex and deprivation quintiles

	England		IMDQ1		IMDQ2		IMDQ3		IMDQ4		IMDQ5	
	2000	**2007**	**2000**	**2007**	**2000**	**2007**	**2000**	**2007**	**2000**	**2007**	**2000**	**2007**
Smoking prevalence (%)												
Male	27.2	23.6	19.2	16.6	22.7	19.6	26.7	23.0	31.0	26.9	36.0	31.2
Female	23.4	19.9	17.2	14.7	20.0	17.0	22.9	19.5	26.2	22.2	29.9	25.2
Diabetes prevalence (%)												
Male	3.7	6.5	3.3	5.7	3.5	6.1	3.7	6.5	3.6	6.1	4.5	8.1
Female	2.9	4.8	2.5	4.1	2.3	3.6	2.6	4.2	3.0	5.2	4.0	6.8
Physical inactivity (%)												
Male	80.9	74.0	81.3	74.5	79.6	72.9	80.4	73.6	80.5	73.6	82.7	75.5
Female	82.4	78.1	82.3	78.0	82.5	78.3	81.6	77.4	81.9	77.7	83.9	79.5
Systolic blood pressure, mmHg												
Male	133.1	130.6	133.1	130.5	133.4	130.8	133.3	130.7	133.0	130.6	133.0	130.6
Female	131.0	125.6	130.7	125.3	131.6	126.6	131.2	125.7	131.1	125.6	130.6	125.1
Cholesterol, mmol/L												
Male	5.6	5.4	5.6	5.4	5.6	5.5	5.6	5.4	5.5	5.4	5.5	5.4
Female	5.7	5.5	5.7	5.6	5.8	5.6	5.7	5.5	5.6	5.4	5.6	5.5
Body mass index, kg/m^2												
Male	27.3	27.7	27.2	27.6	27.4	27.8	27.4	27.7	27.5	27.8	27.1	27.4
Female	26.9	27.2	26.3	26.5	26.7	26.9	27.0	27.2	27.2	27.5	27.6	27.9
Fruit and vegetable consumption, portions per day												
Male	3.4	3.7	3.7	4.1	3.6	4.0	3.4	3.8	3.2	3.5	2.8	3.2
Female	3.6	4.0	4.0	4.4	3.8	4.3	3.6	4.0	3.4	3.8	3.0	3.3

Tables A4-5. Model fit by age, sex and deprivation quintiles

	England	IMDQ1	IMDQ2	IMDQ3	IMDQ4	IMDQ5
Male	71%	67%	68%	69%	74%	79%
Female	114%	101%	108%	112%	121%	134%
Male 25-34	225%	17%	45%	43%	63%	233%
Male 35-44	77%	32%	47%	189%	301%	71%
Male 45-54	34%	36%	36%	33%	33%	35%
Male 55-64	69%	60%	66%	63%	67%	85%
Male 65-74	66%	63%	64%	65%	68%	70%
Male 75-84	75%	70%	75%	69%	80%	82%
Male 85+	84%	77%	70%	88%	91%	105%
Female 25-34	146%	85%	35%	281%	108%	104%
Female 35-44	86%	68%	58%	34%	58%	84%
Female 45-54	72%	128%	113%	63%	59%	68%
Female 55-64	60%	54%	57%	80%	63%	52%
Female 65-74	104%	97%	95%	92%	105%	130%
Female 75-84	108%	91%	111%	106%	112%	125%
Female 85+	141%	118%	118%	139%	164%	212%
Total	**89%**	**81%**	**85%**	**87%**	**94%**	**102%**

% Model fit = ABSOLUTE (1- ((total DPPs – model DPPs)/total DPPs)) × 100

Table A4-6. Uncertainty analysis: parameter distributions use in the probabilistic sensitivity analysis

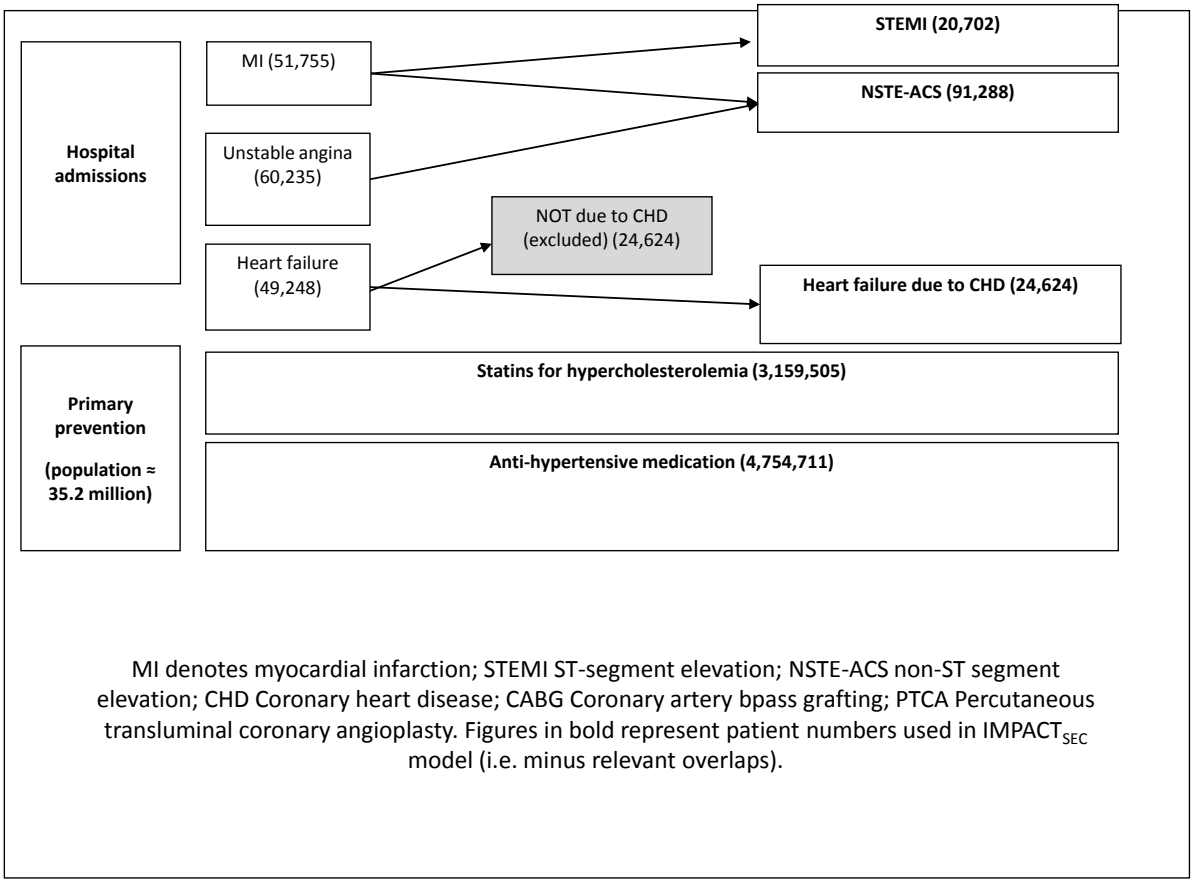
Parameter	Distribution
Population and deaths	
counts	Poisson
Risk Factors	
Prevalence	beta
Continuous	Normal
Relative Risk	Erzats RR
Beta coefficients	Normal
Treatments	
Eligible patients	Poisson
Uptake	beta
Relative Risk Reduction	Erzats RR
Case fatality rate	beta

Table A4-7: Main assumptions and overlap adjustments used in the IMPACTSEC model

Treatment category	Assumptions and overlap adjustments	Justification
Post-AMI	Assume 30% already counted in the heart failure in community group.	Weir (2006)[50]
Post-CABG	Assume two-thirds had AMI, already counted as post AMI	Unal (2004)[1]
Post-angioplasty	Assume 50% had prior AMI, already counted as post AMI Assume 25% also had CABG, thus already counted as post CABG Assume 25% had prior PCI, i.e. repeat procedures, already counted	Unal (2004)[1]
Angina in the community	Start with the total numbers with angina in the community (without MI) based on GPRD prevalence. Then deduct persons counted elsewhere: Persons already treated for unstable angina in hospital 50% of those in the heart failure in the community group 2/3 of those receiving secondary prevention post CABG/post PCI	Capewell (2000)[3]
Heart failure in the community	Based on GPRD prevalence. Assume 50% of heart failure is due to CHD Deduct persons treated for severe heart failure in the hospital (already counted)	NHANES 1999-2000
Fall in population blood pressure	Estimate the number of DPPs by hypertension treatment Then subtract this from the total DPPs attributed to the secular fall in population blood pressure	Capewell (1999)[4] Capewell (2000)[4]
Fall in population total cholesterol	Estimate the number of DPPs by cholesterol lowering medication Then subtract this from the total DPPs attributed to the secular fall in population cholesterol	

AMI denotes acute myocardial infarction, CABG coronary artery bypass graft surgery, CHD coronary heart disease, DPPs deaths prevented or postponed, GPRD General Practice Research Database

Figure A4-1: Patient overlaps for $IMPACT_{SEC}$ (2007)



MI denotes myocardial infarction; STEMI ST-segment elevation; NSTE-ACS non-ST segment elevation; CHD Coronary heart disease; CABG Coronary artery bpass grafting; PTCA Percutaneous transluminal coronary angioplasty. Figures in bold represent patient numbers used in $IMPACT_{SEC}$ model (i.e. minus relevant overlaps).

Secondary prevention	Post MI TOTAL(807,988)	**MI, no HF (565,592)**	Overlap with HF in community (807,988 × 0.3)		
	Angina, no MI TOTAL (1,168,737)	**Angina, no MI (984,807)**	Overlap with HFin community (172,770 × 0.5)	Overlap with post revasc (40,903 + 71,027) × (1/3)	Admissions for UA (60,235)
	HF in the community TOTAL (394,789)	**CHD related HF (172,770)**	Not CHD (394,789 × 0.5) NOT INCLUDED	Admissions for CHD related HF (24,624)	
	Post CABG survivors TOTAL (122,708)	**Survivors†, no AMI, over 7 year period (40,903)**	Overlap with Post MI (122,708 × (2/3))		
	Post PTCA survivorsTOTAL (252,540)	**Survivors†, no AMI, over 7 year period (71,027)**	Overlap with Post MI (252,540 × 0.5)	Overlap with CABG (252,540 × 0.5 × 0.75)	Repeat PTCA procedures (252,540 × 0.5 × 0.75 × 0.75)

AMI denotes acute myocardial infarction; CHD Coronary heart disease; HF heart failure; CABG Coronary artery bpass grafting; PTCA Percutaneous transluminal coronary angioplasty. † MI & unstable angina admissions having PTCA/CABG in 2007 subtracted from revascularisation counts. Figures in bold represent patient numbers used in $IMPACT_{SEC}$ model (i.e. minus relevant overlaps).